Therapeutic Class Overview
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary:
The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-6] Daklinza® (daclatasvir) is a once-daily NS5A inhibitor indicated for use with an NS5B polymerase inhibitor Sovaldi® (sofosbuvir) for 12 weeks in the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection. It is the first Food and Drug Administration (FDA)-approved all-oral regimen for the HCV genotype 3 infection that does not require co-administration of interferon or ribavirin.[1] Technivie® (ombitasvir/paritaprevir/ ritonavir) in combination with ribavirin is the first interferon-free Food and Drug Administration (FDA)-approved drug for the treatment of HCV genotype 4 infection.[6]

HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[8,9] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[10] These agents act via several different mechanisms of action to exert their therapeutic effect.[1-7] Daclatasvir (Daklinza) binds to the N-terminus of NS5A, a nonstructural protein encoded by HCV, and inhibits both viral ribonucleic acid (RNA) replication and virion assembly.[1] Simeprevir (Olysio®) works via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b, thus preventing replication of HCV host cells.[2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The three combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie®), and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Technivie® and Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-6] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 1.

Efficacy of these agents have been established in multiple clinical trials with numerous clinical trials still underway.[11-33] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[33] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations.[33-35] Currently, there are no generic direct-acting antivirals available.

Table 1. Current Medications Available in Therapeutic Class[1-7]

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agents			
Daclatasvir (Daklinza®)	Treatment of chronic HCV genotype 3 in combination with sofosbuvir	Tablet: 30 mg 60 mg	-
Simeprevir (Olysio®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and	Capsule: 150 mg	-

Generic (Trade Name)	FDA Approved Indications	Dosage Form/Strength	Generic Availability
	ribavirin or in combination with sofosbuvir*		
Sofosbuvir (Sovaldi®)	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin or ribavirin alone; treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin; prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection	Tablet: 400 mg	-
Combination Products			
Ledipasvir/sofosbuvir (Harvoni®)	Treatment of chronic HCV genotype 1 infection in adults	Tablet: 90/400 mg	-
Ombitasvir/paritaprevir /ritonavir & dasabuvir (Viekira Pak®)	Treatment of chronic HCV genotype 1 infection in adults	Tablet (dasabuvir): 250 mg Tablet (ombitasvir/ paritaprevir/ ritonavir): 12.5/75/50 mg	-

FDA=Food and drug administration, HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Although simeprevir is FDA-approved for combination therapy with sofosbuvir, the indication is only included on the FDA-approved label of simeprevir and is not listed in sofosbuvir's label.

Evidence-based Medicine

- The efficacy of simeprevir (Olysio®) in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2]
  - In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%; P value not reported).[2]
- The safety and efficacy of simeprevir in combination with sofosbuvir with or without ribavirin for the treatment of hepatitis C genotype 1 was evaluated in the COSMOS trial. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,18]
  - SVR at 12 weeks post therapy (SVR12) was achieved in 92% of the patients in the the intention to treat (ITT) population. SSVR12 for Cohort 1 and Cohort 2 were 90% (95% CI, 81 to 96) and 94% (95% CI, 87 to 98), respectively. The results were not significantly altered by use of ribavirin, duration of treatment, or treatment history (no P values reported).[20]
- The FDA approval of sofosbuvir was based on the results of five phase III trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase III trial (N=223) in HCV/HIV-1 co-infected patients (HCV genotype 1, 2 or 3).[3,11,22,23]

  - All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[11,22,23]
  - Sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study.[3,10]
- The FDA approval of combination ledipasvir/sofosbuvir was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels.[4,12,13,17]
  - ION-1 evaluated treatment-naïve patients include patients with cirrhosis; ION-2 evaluated patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor; ION-3 evaluated non-cirrhotic, treatment-naïve patients.[12,13,17]
  - All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.[12,13,17]
- The FDA approval of ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak®) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). All studies included at least one treatment arm with ribavirin, while several studies included treatment arms without ribavirin.[5,14-16,19,20]
  - Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II).[14-16,19,20]
  - Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of thearpy.[14-16,19,20] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[16]

Key Points within the Medication Class

- American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their guideline.[33]
- Old standards of therapy, including pegylated interferon alfa and ribavirin dual therapy and pegylated interferon alfa, ribavirin along with a protease inhibitor triple therapy are no longer recommended.
- Current, first-line therapies recommended in the new guidelines include all-oral combination therapies, each of which generally has at least one polymerase inhibitor and one other direct-acting agent that acts via a different mechanism of action.
- Depending on genotype, previous treatment-experience and special populations, the recommended regimens and durations of treatment vary due to differences in efficacy provided by clinical trials.
  - For genotype 1, four regimens with similar efficacy are recommended. Duration and addition of ribavirin depend on cirrhosis status and/or previous treatment failures.
    - Daclatasvir 60 mg daily (QD) + sofosbuvir 400 mg QD ± ribavirin for 12 to 24 weeks
    - Ledipasvir/sofosbuvir 90/400 mg QD ± ribavirin for 12 to 24 weeks
    - Paritaprevir/ritonavir/ombitasvir 150/100/25 mg QD + dasabuvir 250 mg twice-daily (BID) ± ribavirin for 12 to 24 weeks
    - Sofosbuvir 400 mg QD + simeprevir 150 mg QD ± ribavirin for 12 to 24 weeks
  - For genotype 2, sofosbuvir 400 mg QD + ribavirin for 12 weeks (16 weeks with cirrhosis), regardless of previous treatment experience is recommended as first-line

        - Daclatasvir 60 mg QD + sofosbuvir (4000 mg) for 12 weeks is recommended for genotype 2 patients who cannot tolerate ribavirin.
    - For genotype 3, first-line regimens recommended include:
        - Daclatasvir (60 mg) and sofosbuvir (400 mg) ± ribavirin for 12 to 24 weeks
        - sofosbuvir 400 mg QD + ribavirin + weekly peginterferon for 12 weeks
    - For Genotype 4, three regimens are recommended, two of which are recommended independent of cirrhosis status and treatment experience and one of which is based on previous treatment failure.
        - Ledipasvir/sofosbuvir 90/400 mg QD for 12 weeks
        - Paritaprevir/ritonavir/ombitasvir 150/100/25 QD + ribavirin for 12 weeks
        - Sofosbuvir 400 mg QD + ribavirin for 24 weeks (treatment-naïve) or sofosbuvir 400 mg QD + weight-based ribavirin for 24 weeks (previous treatment failure; may use for 12 weeks if pegylated interferon alfa added).
    - In patients that fail a sofosbuvir, daclatasvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir plus dasabuvir, it is recommended to defer therapy if they have minimal liver disease; guidelines do not offer a specific regimen for recipients with extensive liver disease, but recommend resistance-testing. They recommend treatment for at least 24 weeks use of ribavirin if not contraindicated.

- Other Key Facts:
    - Prior to initiating therapy with simeprevir in combination with peginterferon and ribavirin, patients with HCV genotype 1a should be screened for the presence of NS3 Q80K polymorphism.[2]
        - Screening for NS3 Q80K polymorphism is not necessary when used in combination with sofosbuvir that is associated with substantially reduced drug efficacy; alternative therapy should be considered if this polymorphism is present.[2]
    - When prescribing ombitasvir/paritaprevir/ritonavir (Technivie®) or ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®), screening for drugs that should not be coadministered is recommended due to many, often severe, drug interactions.[5]
    - Lack of data on the use of Technivie® or Viekira Pak® with or without ribavirin in cirrhotic patients with HCV genotype 4 infection (guidelines recommend 24-week treatment).[5,6]
    - Dose of daclatasvir must be adjusted when given with strong CYP3A inhibitors (30 mg QD) and moderate CYP3A inducers (90 mg QD).[1]
        - Two 30 mg tablets or one 30 mg and one 60 mg tablet must be used to make a 90 mg dose.

References

1. Daklinza® [package insert]. Princeton (NJ): Bristol-Myers Squibb Company; 2015 July [cited 2015 July 30]. Available from: http://packageinserts.bms.com/pi/pi_daklinza.pdf.
2. Olysio® [package insert]. Titusville (NJ): Janssen Therapeutics; 2014 Nov.
3. Sovaldi® [package insert]. Foster City (CA): Gilead Sciences, Inc.; 2014 Nov.
4. Harvoni® [package insert]. Foster City (CA): Gilead Sciences, Inc.; 2014 Oct.
5. Viekira Pak® [package insert]. North Chicago (IL): AbbVie; 2014 Dec.
6. Technivie® [package insert on the internet]. North Chicago (IL): AbbVie; 2015 July [cited 2015 Aug 4]. Available from: https://www.technivie.com/.
7. Micromedex® 2.0 [database on the Internet]. Greenwood Village (CO): Truven Health Analytics; Updated periodically [cited 2015 Jan 21]. Available from http://www.micromedexsolutions.com/.
8. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep. 2010 Dec 17;59(RR-12):1-110.
9. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, Management and treatment of hepatitis C; An Update. 2009. Hepatology 2009; 49(4):1-40.
10. Ng J, Wu J. Hepatitis B- and hepatitis C-related hepatocellular carcinomas in the United States: similarities and differences. Hepat Mon. 2012 Oct;12(10 HCC):e7635.
11. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.
12. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98.
13. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.
14. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1594-603.

15. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014 May 22;370(21):1983-92.
16. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014 May 22;370(21):1973-82.
17. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.
18. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014 Jul 26. pii: S0140-6736(14)61036-9.
19. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1604-14.
20. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV Genotype 1b Infection. Gastroenterology. 2014 May 9.
21. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014 Dec 18;371(25):2375-82.
22. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 May 16;368(20):1867-77.
23. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes
24. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015 Apr;61(4):1127-35.
25. Bristol-Myers Squibb. Safety and Efficacy Study of Daclatasvir 60mg, Sofosbuvir 400mg, and Ribavirin (Dosed Based Upon Weight) in Subjects With Chronic Genotype 3 Hepatitis C Infection With or Without Prior Treatment Experience and Compensated Advanced Cirrhosis for 12 or 16 Weeks. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02319031 NLM Identifier: NCT02319031.
26. Hézode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015 Jun 20;385(9986):2502-9.
27. AbbVie. A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir Co-administered With Ribavirin (RBV) in Adults With Genotype 4 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (AGATE-1). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02265237 NLM Identifier: NCT02265237.
28. AbbVie. A Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Ribavirin in Adults with Genotype 1 and Ombitasvir/Paritaprevir/Ritonavir with Ribavirin in Adults with Genotype 4 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis (TURQUOISE-CPB). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02219477 NLM Identifier: NCT02219477.
29. AbbVie. Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir in Adults with Genotype 1a or Genotype 4 Chronic Hepatitis C Virus (HCV) Infection, with Severe Kidney Impairment or End Stage Kidney Disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02487199 NLM Identifier: NCT02487199.
30. AbbVie. Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir in Adults with Genotype 1a or Genotype 4 Chronic Hepatitis C Virus (HCV) Infection, With Severe Kidney Impairment or End Stage Kidney Disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02487199 NLM Identifier: NCT02487199.
31. AbbVie. A Study to Evaluate Treatment of Hepatitis C Virus Infection in Pediatric Subjects (Zircon). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02486406 NLM Identifier: NCT02486406.
32. AbbVie. A Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/r with or without Dasabuvir and with Ribavirin in Chronic Hepatitis C Virus Genotype 1 or 4 Infected Adults with Successfully Treated Early Stage Hepatocellular Carcinoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02504099 NLM Identifier: NCT02504099.
33. American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), International Antiviral Society-USA (IAS-USA). Recommendations for testing, managing, and treating hepatitis C [guideline on the Internet]. Alexandria (VA): AASLD/IDSA/IAS-USA 2015 Aug [cited 2015 Aug 10]. Available at: http://www.hcvguidelines.org.
34. Department of Veteran Affairs National Hepatitis C Resource Center Program and the Office of Public Health. Chronic hepatitis C Virus (HCV) infection: Treatment considerations [guideline on the Internet]. Washington (DC): VA 2015 July [cited 2015 July 31]. Available at: http://www.hepatitis.va.gov/pdf/treatment-considerations-2015-07.pdf.
35. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015 Jul;63(1):199-236.

Therapeutic Class Review
Direct Acting Hepatitis C Antivirals and Combinations

Overview/Summary

The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-6] Daklinza® (daclatasvir) is a once-daily NS5A inhibitor indicated for use with an NS5B polymerase inhibitor Sovaldi® (sofosbuvir) for 12 weeks in the treatment of patients with chronic hepatitis C virus (HCV) genotype 3 infection. It is the first Food and Drug Administration (FDA)-approved all-oral regimen for the HCV genotype 3 infection that does not require co-administration of interferon or ribavirin.[1] Technivie® (ombitasvir/paritaprevir/ritonavir) in combination with ribavirin is the first interferon-free Food and Drug Administration (FDA)-approved drug for the treatment of HCV genotype 4 infection.[6]

HCV is an enveloped ribonucleic acid virus that is transmitted through exposure with infected blood and is the most common bloodborne infection in the United States, with an estimated prevalence of 3.2 million people chronically infected. Chronic HCV develops in 70 to 85% of HCV-infected persons and is associated with significant morbidity (e.g., cirrhosis, hepatocellular carcinoma [HCC]) and is the leading cause of liver transplantation.[8,9] The average annual incidence rate of HCC in the U.S. between 2001 and 2006 was 3.0 per 100,000 people, with 48% to cases attributed to HCV.[10] These agents act via several different mechanisms of action to exert their therapeutic effect.[1-7] Daclatasvir (Daklinza) binds to the N-terminus of NS5A, a nonstructural protein encoded by HCV, and inhibits both viral ribonucleic acid (RNA) replication and virion assembly.[1] Simeprevir (Olysio®) works via inhibition of the HCV NS3/4A protease of HCV genotype 1a and 1b, thus preventing replication of HCV host cells.[2] Similarly, sofosbuvir (Sovaldi®) inhibits HCV NS5B polymerase which also prevents the replication of HCV host cells, however, it is active against multiple genotypes of HCV.[3] The three combination products that include direct acting hepatitis C antivirals include ledipasvir/sofosbuvir (Harvoni®), ombitasvir/paritaprevir/ritonavir (Technivie®), and a 4-drug regimen of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®). Paritaprevir and dasabuvir exert their mechanisms of action in the same was as other agents and inhibit NS3/4A protease and NS5B polymerase, respectively. Ledipasvir and Ombitasvir work along the same line as the other agents, but specifically inhibit HCV non-structural protein NS5A. Ritonavir, when used in Technivie® and Viekira Pak®, is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus.[4-6] Specific indications for each of the direct acting hepatitis C antiviral agents are listed in Table 2.

Efficacy of these agents have been established in multiple clinical trials with numerous clinical trials still underway.[11-33] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[33] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations. These regimens along with other clinical guidelines are summarized in Table 12.[33-35] Currently, there are no generic direct-acting antivirals available.

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Daclatasvir (Daklinza®)	HCV NS5A inhibitor	-
Simeprevir (Olysio®)	NS3/4A protease inhibitor	-
Sofosbuvir (Sovaldi®)	NS5B polymerase inhibitor	-
Combination Products		

Generic Name (Trade name)	Medication Class	Generic Availability
Ledipasvir/sofosbuvir (Harvoni®)	HCV NS5A inhibitor/ NS5B polymerase inhibitor	-
Ombitasvir/paritaprevir/ritonavir/ dasabuvir (Viekira Pak®)	HCV NS5A inhibitor/ NS3/4A protease inhibitor/ CYP3A4 inhibitor* & NS5B polymerase inhibitor	-
Ombitasvir/paritaprevir/ritonavir (Technivie®)	HCV NS5A inhibitor/ NS3/4A protease inhibitor/ CYP3A4 inhibitor*	-

*Ritonavir is used as a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir and overall drug exposure; it has no direct effect on hepatitis C virus

Indications

Table 2. Food and Drug Administration Approved Indications[1-7]

Indication	Daclatasvir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Ombitasvir/ paritaprevir/ ritonavir
Treatment of chronic HCV genotype 1 infection in adults				a	a	
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin		a	a			
Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with sofosbuvir		a *				
Treatment of chronic HCV genotype 1 in combination with ribavirin alone (without peginterferon alfa)			a			
Treatment of chronic HCV genotype 3 in combination with sofosbuvir	a †					
Treatment of chronic HCV genotype 4 in combination with ribavirin, in patients without cirrhosis.						a
Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin			a			
Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin			a			
Prevention of post-transplant HCV reinfection in combination with ribavirin in patients with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection			a			

HCV=hepatitis C virus, HIV=human immunodeficiency virus
*Although simeprevir is FDA-approved for combination therapy with sofosbuvir, the indication is only included on the FDA-approved label of simeprevir and is not listed in sofosbuvir's label.
†Sustained virologic response (SVR) rates are reduced in HCV genotype 3-infected patients with cirrhosis receiving daclatasvir in combination with sofosbuvir for 12 weeks.

Pharmacokinetics

Table 3. Pharmacokinetics[1-7]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single Entity Products				
Daclatasvir	67	6.6	Not Reported	12 to 15
Simeprevir	Not reported	<1	None	41
Sofosbuvir	Not reported	80	GS-461203	0.5
Combination Products				
Ledipasvir/ sofosbuvir	Not reported	<1/80	GS-461203 (sofosbuvir)	47
Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Not reported	1.91 (ombitasvir)/ 8.8 (paritaprevir)/ 11.3 (ritonavir)/ 2 (dasabuvir)	None	21 to 25 (ombitasvir)/ 5.5 (paritaprevir)/ 4 (ritonavir)/ 5.5 to 6 (dasabuvir)
Ombitasvir/ paritaprevir/ ritonavir	48.1 (ombitasvir)/ 52.6 (paritaprevir)/ Not Reported (ritonavir)	1.91 (ombitasvir)/ 8.8 (paritaprevir)/ 11.3 (ritonavir)/	None	21 to 25 (ombitasvir)/ 5.5 (paritaprevir)/ 4 (ritonavir)/

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the direct acting hepatitis C antivirals are outlined in Table 4.[11-32] Overall, data from clinical trials support the FDA-approved indications and dosing recommendations for these agents.

The efficacy of simeprevir (Olysio®) in patients with HCV genotype 1 infection was evaluated in several unpublished studies, including two phase III trials in treatment-naïve patients (QUEST 1 and QUEST 2), one phase III trial in patients who relapsed after prior interferon-based therapy (PROMISE).[2] QUEST 1 and QUEST 2 were similarly designed, randomized, double-blind, placebo-controlled, two-arm, multicenter trials in which patients were treated with simeprevir for 12 weeks or placebo plus peginterferon afla-2a (QUEST 1 and 2) or peginterferon alfa-2b (QUEST 2) and ribavirin. In the pooled analysis of QUEST 1 and QUEST 2, a greater proportion of patients in the simeprevir group achieved SVR at 12 weeks (SVR12) compared to control group (80 vs 50%). In the simeprevir group, SVR12 rates were lower in patients with genotype 1a virus with the NS3 Q80K polymorphism at baseline (58%) compared to those without the Q80K polymorphism (84%). The corresponding SVR12 rates in the control group were 52 and 43%, respectively.[2] In PROMISE, a greater proportion of patients in the simeprevir group achieved SVR12 compared to control group (79 vs 37%). Again, patients with the genotype 1a virus with the NS3 Q80K polymorphism had lower SVR12 rates than those without it (47% compared to 78%, corresponding SVR12 rates in the control group were 30 and 26% respectively).[2]

The safety and efficacy of simeprevir in combination with sofosbuvir was evaluated in the COSMOS trial, a randomized, open-label, phase IIa trial evaluating a once daily combination of simeprevir 400 mg and sofosbuvir 150 mg with and without ribavirin for 12 and 24 weeks in HCV genotype 1 patients. The four-point score METAVIR scale was used to quantify the degree of inflammation and fibrosis of the liver. Cohort 1 included prior null responders with METAVIR scores F0 to F2 and Cohort 2 included prior null responders and treatment-naïve patients with METAVIR scores F3 to F4.[2,18] One hundred fifty-four (92%) of 167 of patients in the intention-to-treat (ITT) population achieved SVR12, 90% (95% CI, 81 to 96) in Cohort 1 and 94% (95% CI, 87 to 98) in Cohort 2. The results were not significantly altered by use of ribavirin, duration of treatment, or by use of previous treatment (P value not reported). No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir.[18]

The FDA approval of sofosbuvir (Sovaldi®) was based on the results of five phase 3 trials (N=1,724) in HCV mono-infected patients (genotypes 1 to 6) and one unpublished phase 3 trial (N=223) in HCV/HIV-1 co-infected patients (HCV genotype 1, 2 or 3). Sofosbuvir dose was 400 mg daily, ribavirin dose was weight-

based at 1,000 to 1,200 mg daily in two divided doses when given with sofosbuvir, and the peginterferon alfa dose was 180 µg weekly. Treatment duration was fixed in each trial and was not guided by patients' HCV RNA levels. All trials utilized SVR12 as the primary endpoint and overall, these studies showed that sofosbuvir provided a significant improvement in SVR12 compared with control in both treatment-naïve and treatment-experienced patients.[11,22,23] However, sofosbuvir was not specifically studied in treatment-experienced patients with HCV genotype 1 infection. According to the prescribing information, the estimated response rate in patient who previously failed treatment with peginterferon alfa and ribavirin is 71%. This is based on the observed response rate in patients from the NEUTRINO study with multiple baseline factors associated with a lower response to interferon-based treatment (i.e., IL28B non-C/C alleles, HCV RNA >800,000 IU/mL and F3 to F4 fibrosis).[3,11,22,23]

The FDA approval of combination ledipasvir/sofosbuvir (Harvoni®) was based on the results of three phase III trials (N=1,518) in HCV mono-infected subjects with genotype 1 infection who had compensated liver disease. All three phase III trials evaluated efficacy of ledipasvir 90 mg/sofosbuvir 400 mg fixed-dose tablet administered once daily with or without ribavirin.[4] Treatment duration was fixed in each trial and was not guided by subjects' HCV RNA levels. All trials were randomized, open-label studies that evaluated SVR12 as the primary endpoint.[12,13,17] The different populations studied include treatment-naïve patients include patients with cirrhosis (ION-1), patients with or without cirrhosis who failed previous therapy with an interferon-based regimen including those containing an HCV protease inhibitor (ION-2), and non-cirrhotic, treatment-naïve patients (ION-3). All studies showed that ledipasvir/sofosbuvir significantly improved SVR12 rate compared to control.[12,13,17]

The FDA approval of ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak®) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). These included the SAPPHIRE-I (double-blind), SAPPHIRE-II (double-blind), PEARL-II (open-label), PEARL-III (open-label), PEARL-IV (double-blind) and TURQUIOSE-II (open-label).[14-16,19,20] Each study used SVR12 as the primary endpoint and evaluated ombitasvir/paritaprevir/ritonavir once-daily added to dasabuvir twice-daily. All trials had a treatment arm that contained ribavirin added to ombitasvir/paritaprevir/ritonavir/dasabuvir, with the PEARL studies (II, III and IV) also having a treatment arm without ribavirin. Study populations for each of the studies include treatment-naïve, non-cirrhotic adults with HCV genotype 1 infection (SAPPHIRE-I), treatment-naïve, non-cirrhotic adults with HCV genotype 1b and HCV genotype 1a infections (PEARL-III and PEARL-IV, respectively), treatment-naïve or previously treated with peginterferon alfa and ribavirin cirrhotic adults with HCV genotype 1 infection (TURQUOISE-II), noncirrhotic adults with HCV genotype 1 infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (SAPPHIRE-II) and finally, non-cirrhotic adults with HCV genotype 1b infection who either relapsed or were nonresponders to prior peginterferon alfa and ribavirin therapy (PEARL-II). Overall, SVR12 rates were high and significantly improved compared with control after 12 weeks of thearpy.[14-16,19,20] Only TURQUOISE-II evaluated patients beyond 12 weeks of therapy and found there was no difference between 12 weeks of therapy compared with 24 weeks of therapy (P=0.09).[16]

The FDA approval of Daklinza® (daclatasvir) was based on the results of ALLY-3 (N=152), a phase III, open-label study evaluating 12 week regimen of daclatasvir 60 mg plus sofosbuvir 400 mg in treatment-naive and treatment-experienced patients with chronic HCV genotype 3 infection. The primary endpoint was the SVR at post treatment week 12 (SVR12). High SVR12 rates were observed among patients without cirrhosis: 97% (73/75) and 94% (32/34) in treatment-naïve and treatment-experienced patients, respectively. In contrast, SVR12 rates in cirrhotic patients were much lower: 58% (11/19) and 69% (9/13) in treatment-naïve and treatment-experienced patients, respectively.[24] An ongoing randomized phase III study is evaluating a combination of daclatasvir, sofosbuvir and ribavirin for 12 or 16 weeks to determine whether the addition of ribavirin or extending treatment duration improved SVR rates in cirrhotic patients with HCV genotype 3 infection.[25]

The FDA-approval of Technivie® (ombitasvir/paritaprevir/ritonavir) in the treatment of HCV genotype 4 was based on the results of an open-label, randomized, multicenter phase IIb PEARL-I study (N=135). The study evaluated ombitasvir/paritaprevir/ritonavir with or without ribavirin in patients with chronic HCV genotype 4 infection and no cirrhosis. Patients were either treatment-naïve or treatment experienced (prior failure of

peginterferon alfa and ribavirin). In treatment-naive patients, the SVR12s were 100% (42/42) in the ribavirin-containing regimen and 90.9% (40/44) in the ribavirin-free regimen. In the treatment-naive group without ribavirin, on-treatment virologic breakthrough was reported in one patient (2%), two patients (5%) experienced post-treatment relapse, and one patient (2%) was lost to follow-up. All 49 treatment-experienced patients in the ribavirin-containing group achieved SVR12.[26] AGATE-I is an ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 12, 16 or 24 weeks in cirrhotic patients with HCV genotype 4 infection, including treatment-naïve patients and those who have failed peginterferon alfa and ribavirin or sofosbuvir-containing regimens.[27] TURQUOISE-CPB is another ongoing phase III study evaluating ombitasvir/paritaprevir/ritonavir with ribavirin for 24 weeks in patients with HCV genotype 4 infection and decompensated cirrhosis.[28] Several other studies are planned or recruiting patients to evaluate ombitasvir/paritaprevir/ritonavir with or without ribavirin in less well studied subpopulations with HCV genotype 4 infection, including severe renal disease, children (three to 17 years old), and status post successful treatment of early stage hepatocellular carcinoma.[29-32]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment of Genotype 1, 2, 3, 4, 5, and 6 Chronic Hepatitis: Treatment-Naïve Patients				
Lavitz et al[11] (NEUTRINO and FISSION) NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks and peginterferon alfa-2a 180 µg once weekly for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection FISSION: AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 mg/day in two divided doses for 24 weeks	infection			Secondary: Not reported
Afdhal et al[12] (ION 1) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not previously received treatment for HCV infection	N=865 12 to 24 weeks	Primary: SVR12 Secondary: Not reported	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR rates were 99% (95% CI, 96 to 100) in the group that received 12 weeks of ledipasvir/sofosbuvir; 97% (95% CI, 94 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 98% (95% CI, 95 to 99) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 97 to 100) in the group that received 24 weeks of ledipasvir/ sofosbuvir with ribavirin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Kowdley et al[13] (ION 3) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 8 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection without cirrhosis who had not previously received treatment for HCV infection	N=647 8 to 12 weeks	Primary: SVR12 Secondary: Noninferiority of eight weeks of ledipasvir/ sofosbuvir to the other treatment regimens	Primary: The SVR12 rates in all four treatment groups were higher than the historical rate of 60% (P<0.001 for all comparisons). The SVR12 rate was 94% (95% CI, 90 to 97) with eight weeks of ledipasvir/sofosbuvir, 93% (95% CI, 89 to 96) with eight weeks of ledipasvir/sofosbuvir with ribavirin, and 95% (95% CI, 92 to 98) with 12 weeks of ledipasvir/sofosbuvir. Secondary: Treatment with ledipasvir/sofosbuvir for eight weeks was noninferior to both the 8-week ledipasvir/sofosbuvir + ribavirin treatment arm (treatment difference 0.9%; 95% CI, -3.9 to 5.7%) and the 12-week ledipasvir/sofosbuvir treatment arm (treatment difference -1.4%; 95% CI, -6.4 to 3.6%).
Feld et al[14] (SAPPHIRE-I) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	N=631 12 weeks	Primary: SVR12 Secondary: Normalization of the alanine aminotransferase level, SVR12 by HCV subtype (1a or 1b), virologic failure during	Primary: The SVR12 rate in group A (96.2%; 95% CI, 94.5 to 97.9) was statistically noninferior and superior to the calculated historical control rate of 78% (95% CI, 75 to 80) in treatment-naïve patients without cirrhosis who received telaprevir and PEG/RBV. Secondary: The SVR12 rate was 95.3% (95% CI, 93.0 to 97.6) among patients with HCV genotype 1a infection and 98.0% (95% CI, 95.8 to 100) among those with HCV genotype 1b infection. These rates were statistically superior to the historical control rates in the respective subgroups (72%; 95% CI, 68 to 75 in patients with HCV genotype 1a infection and 80%; 95% CI, 75 to 84 in those with HCV genotype 1b infection).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks (Group A) vs placebo for 12 weeks of double-blind period followed by active regimen as open-label therapy for 12 weeks (Group B)			treatment, and posttreatment relapse	The rate of normalization of the alanine aminotransferase level was 97.0% in group A as compared with 14.9% in group B (P<0.001). Virologic failure during treatment and relapse after treatment occurred in 0.2% and 1.5%, respectively, of the patients in group A.
Ferenci et al[15] (PEARL-III and PEARL-IV) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily	DB, MC, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection (PEARL-III) or HCV genotype 1a infection (PEARL-IV), no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	PEARL-III N=419 12 weeks PEARL-IV N=305 12 weeks	Primary: SVR12 Secondary: Superiority of the SVR12 rate at each group as compared with the historical rate with telaprevir plus PEG/RBV, noninferiority of the SVR12 rate in the groups that did and did not receive ribavirin, hemoglobin level below the	Primary: In the genotype 1a study, the SVR12 rates were 97.0% (95% CI, 93.7 to 100) in patients who received the regimen with ribavirin and 90.2% (95% CI, 86.2 to 94.3) in patients who received the regimen without ribavirin. In the genotype 1b study, the SVR12 rates were 99.5% (95% CI, 98.6 to 100.0) in patients who received the regimen with ribavirin and 99.0% (95% CI, 97.7 to 100.0) in patients who received the regimen without ribavirin. Secondary: In the genotype 1a study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV in treatment-naïve adults with HCV genotype 1a infection and no cirrhosis. The regimen without ribavirin did not meet the noninferiority criterion as compared with the regimen with ribavirin, because the lower boundary of the CI for the difference (-6.8%; 95% CI, -12.0 to -1.5) crossed the noninferiority margin of 10.5%. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups. In the genotype 1b study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV among previously untreated adults with HCV genotype 1b infection and no cirrhosis. In addition, the SVR

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and placebo			lower limit of the normal range at the end of treatment, and the percentage of patients in each group with virologic failure during treatment or relapse after treatment	rate among patients who did not receive ribavirin was noninferior to the rate among those who received ribavirin (difference, -0.5%; 95% CI, -2.1 to 1.1). Among the patients in the genotype 1a study who had a hemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a hemoglobin level below the lower limit of the normal range at the end of treatment (P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). Among patients with genotype 1a infection, the rate of virologic failure was higher in the ribavirin-free group than in the group receiving ribavirin (7.8 vs 2.0%). Of patients with genotype 1b infection, none had virologic failure in the ribavirin-free group and one had virologic failure (0.48%) in the group receiving ribavirin.
Poordad et al[16] (TURQUOISE-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, treatment-naïve or previously treated with PEG/RBV, documented cirrhosis by means of liver biopsy, Child–Pugh class A score <7, no current or past clinical evidence of Child–Pugh class B or C, HCV	N=380 12 to 24 weeks	Primary: SVR12 compared to historical control Secondary: SVR12 with 12- vs 24-week treatment, virologic failure during treatment or relapse after treatment	Primary: The SVR12 rates were 91.8% (97.5% CI, 87.6 to 96.1) in the 12-week group and 95.9% (97.5% CI, 92.6 to 99.3) in the 24-week group. These rates were statistically noninferior and superior to the historical control rate with telaprevir and PEG/RBV among patients with HCV genotype 1 infection and cirrhosis (47%; 95% CI, 41 to 54). Secondary: The difference in the SVR12 rates between the 12- and 24-week treatment groups was not significant (P=0.09). The SVR rates with 12- vs 24-week treatment were 88.6 vs 94.2% in genotype 1a patients; 98.5 vs 100% in genotype 1b patients; 94.2 vs 94.6% in treatment-naïve patients; 96.6 vs 100% in relapsers with prior PEG/RBV; 94.4 vs 100% in prior partial responders to PEG/RBV; and 86.7 vs 95.2% in prior null responders to PEG/RBV. Among patients with HCV genotype 1a infection and a prior null response to PEG/RBV, SVR was achieved in 92.9% (95% CI, 85.1 to 100) in the 24-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks	RNA >10,000 IU/mL, platelets ≥60,000/mm^3, serum albumin ≥2.8 g/dL, total bilirubin <3 mg/dL, INR≤2.3, and serum alpha-fetoprotein ≤100 ng/mL			week group as compared to 80.0% (95% CI, 68.9 to 91.1) in the 12-week group. Virologic failure during treatment or relapse after treatment occurred in 6.2% and 2.3% of patients in the 12-week and 24-week groups, respectively. Virologic failure during treatment occurred 0.5% (95% CI, 0 to 1.4) and 1.7% (95% CI, 0 to 3.7) of patients in the 12-week and 24-week groups, respectively. Significantly more patients in the 12-week group than in the 24-week group had a relapse: 5.9% (95% CI, 2.7 to 9.2) vs 0.6% (95% CI, 0 to 1.8).
Treatment of Genotype 1: Treatment-Experienced Patients				
Afdhal et al[17] (ION 2) Ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks	MC, OL, R Patients ≥18 years of age with chronic HCV genotype 1 infection who had not had a SVR with either PEG/ribavirin or NS3/4A protease inhibitor combined with PEG/ribavirin	N=440 12 to 24 weeks	Primary: SVR12 Secondary: SVR24	Primary: In all four treatment groups, the SVR12 rate was higher than the adjusted historical response rate of 25% (P<0.001 for all comparisons). The SVR12 rates was 94% (95% CI, 87 to 97) in the group that received 12 weeks of ledipasvir/sofosbuvir; 96% (95% CI, 91 to 99) in the group that received 12 weeks of ledipasvir/sofosbuvir with ribavirin; 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir; and 99% (95% CI, 95 to 100) in the group that received 24 weeks of ledipasvir/sofosbuvir with ribavirin. Among patients with cirrhosis who were assigned to 12 weeks of treatment, the SVR12 rates were 86% for those who received ledipasvir/sofosbuvir and 82% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 95% and 100%. Among patients with cirrhosis who were assigned to 24 weeks of treatment, the SVR12 rates were 100% for those who received ledipasvir/sofosbuvir

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks vs ledipasvir 90 mg and sofosbuvir 400 mg once daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks				and 100% for those who received ledipasvir/sofosbuvir with ribavirin; the respective rates among patients without cirrhosis were 99% and 99%. The difference between the SVR rates among patients with cirrhosis who received 12 weeks of treatment and the SVR among patients with cirrhosis who received 24 weeks of treatment was statistically significant (P=0.007). Secondary: All patients who had a SVR12 also had a SVR24. No patient had a relapse after post-treatment week 12.
Lawitz et al[18] COSMOS Cohort 1: Simeprevir 150 mg daily plus sofosbuvir 400 mg daily vs simeprevir 150 mg daily plus sofosbuvir 400 mg daily plus ribavirin 1,000 to 1,200 mg daily (based on body weight) Cohort 2: Simeprevir 150 mg daily plus sofosbuvir 400 mg daily vs	OL, MC, RCT Patients ≥18 years of age with a diagnosis of hepatitis C genotype 1, HCV RNA >10,000 IU/mL and HIV negative Cohort 1: Previous non-responders to peginterferon and ribavirin and no to moderate liver fibrosis Cohort 2: Previous non-	N=167 Cohort 1 N=80 Cohort 2 N=87	Primary: SVR12 Secondary: SVR4, SVR24, rapid virological response, on-treatment failure and viral relapse	Primary: One hundred fifty-four (92%) of 167 of patients in the ITT population achieved SVR12, 90% (95% CI, 81 to 96) in Cohort 1 and 94% (95% CI, 87 to 98) in Cohort 2. The results were not significantly altered by use of ribavirin, duration of treatment, or by use of previous treatment (P value not reported). Secondary: All patients who achieved SVR12 also achieved SVR4. More than 91% of patients overall achieved SVR4. Rapid virological response was achieved in 81% of patients overall, but SVR12 was still achieved in all but one who had detectable HCV RNA titers four weeks after the start of treatment. No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir (Arg155Lys, Asp168Glu, Ile170Thr), but none to sofosbuvir. Five had received 12 weeks of treatment, and four had the HCV Gln80Lys polymorphism at baseline. Viral relapse was not associated with reduced speed of viral decay during weeks one to four of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
simeprevir 150 mg daily plus sofosbuvir 400 mg daily plus ribavirin 1,000 to 1,200 mg daily (based on body weight)	responders to peginterferon and ribavirin or treatment naïve and have severe liver fibrosis			
Zeuzem et al[19] (SAPPHIRE-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs placebo	MC, DB, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection without cirrhosis, relapsers or nonresponders with prior PEG/RBV treatment, and HCV RNA >10,000 IU/mL	N=394 12 weeks	Primary: SVR12 compared to historical control Secondary: Normalization of the alanine aminotransferase level, SVR by HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse	Primary: Treatment with the active-regimen lead to a SVR12 of 96.3% (95% CI, 94.2 to 98.4) which was noninferior and superior to the historical control SVR rate of 65% (95% CI, 60 to 70) among previously treated patients with HCV genotype 1 infection and no cirrhosis who had received retreatment with telaprevir and PEG/RBV (P value not reported). Secondary: The rate of normalization of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9 vs 12.8%, P<0.001). The SVR rates were similar between patients with HCV genotype 1a infection (96.0%; 95% CI, 93.0 to 98.9) and those with HCV genotype 1b infection (96.7%; 95% CI, 93.6 to 99.9). The HCV genotype (1a or 1b) could not be determined for one patient, who had a SVR12. No patient had virologic failure during treatment. Of the 293 patients who completed therapy, 2.4% had a post-treatment viral relapse.
Andreone et al[20] (PEARL-II) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection for at least	N=179 12 weeks	Primary: SVR12 compared to historical control Secondary:	Primary: The SVR12 rate was 96.6% (95% CI, 92.8 to 100) in the group receiving ribavirin and 100% (95% CI, 95.9 to 100) in the group not being treated with ribavirin. These rates were statistically noninferior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks	six months, and HCV RNA >10,000 IU/mL, no cirrhosis, and prior failure of therapy with PEG/RBV		Proportion of patients with decreased hemoglobin level to less than the lower limit of normal at the end of treatment, superiority of both groups to historical SVR rate, noninferiority of both treatment groups, virologic failure during treatment, and post-treatment relapse	Hemoglobin levels less than the lower limit of normal at the end of treatment were more common in patients receiving ribavirin compared to those that did not (42.0 vs 5.5%, respectively; P<0.001), although clinically significant grade 2 hemoglobin level declines to <10 g/dL at the end of treatment occurred in only two patients (1.1%), both in the group receiving ribavirin. The SVR12 rates in the group receiving ribavirin (96.6%) and in the group not being treated with ribavirin (100%) were statistically superior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. The SVR12 rates in the group not receiving ribavirin were noninferior to those in the group receiving ribavirin (difference, 3.4%; 95% CI, -0.4 to 7.2) No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients in the group receiving ribavirin who did not achieve SVR12, there were two patients (2.3%) who discontinued study drug.
Treatment-naïve and -experienced subjects with HCV genotype 1 infection status post liver transplant				
Kwo et al[21] (CORAL-I) ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and	MC, OL Patients 18 to 70 years of age with chronic HCV genotype 1 infection, HCV RNA >10,000 IU/mL who received a liver transplant ≥12 months before screening because	N=34 24 weeks	Primary: SVR12 Secondary: SVR24, virologic failure during treatment, and post-treatment relapse	Primary: The SVR12 rate was 97% (95% CI, 85 to 100). All five patients infected with genotype 1b (100%) and 28 of 29 patients infected with genotype 1a (97%) had a SVR. Secondary: The SVR24 rate was 97% (95% CI, 85 to 100). All the patients also had HCV RNA <25 IU/mL at the end of treatment. One patient did not have a SVR owing to a relapse on post-treatment day three. No relapses occurred after post-treatment week 12.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin (dosing at investigator's discretion) for 24 weeks A stable tacrolimus- or cyclosporine-based immunosuppressive regimen was required, and glucocorticoids were allowed at a dose of ≤5 mg/day.	of chronic HCV infection, and Metavir score≤F2 on liver biopsy performed ≤6 months before screening			
Treatment of Genotype 2 and 3 Chronic Hepatitis C: Treatment-Naïve and Experienced Patients				
Jacobson et al[22] (POSITRON and FUSION) POSITRON: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo FUSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight	POSITRON: DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not candidates for interferon therapy FUSION: AC, DB, MC, R Patients ≥18 years of age with confirmed	POSITRON: N=278 12 weeks FUSION: N=201 12 to 16 weeks	POSITRON: Primary: SVR12 Secondary: Not reported FUSION: Primary: SVR12 Secondary: Not reported	POSITRON: Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%). Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared to 92% without cirrhosis. Secondary: Not reported FUSION: Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks vs sofosbuvir 400 mg once daily for 16 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen			the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001). Response rates in patients with genotype 2 infection who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant. Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection). Secondary: Not reported
Zeuzem et al[23] (VALENCE) Sofosbuvir 400 mg once daily for 12 weeks	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.	chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL during screening			Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported
Treatment of Genotype 3 Chronic Hepatitis C: Treatment-Naïve and Experienced Patients				
Nelson DR et al[24] (ALLY-3) Daclatasvir 60 mg once daily for 12 weeks and sofosbuvir 400 mg once daily for 12 weeks	OL Patients ≥18 years of age (range 24 to 73) with chronic HCV genotype 3 infection who were treatment-naïve or and treatment-experienced (prior interferon alfa with or without ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents,	N=152 12 weeks	Primary: SVR12 Secondary: Proportion of patients achieving HCV-RNA levels <LLOQ detectable or undetectable, at on-treatment weeks 1, 2, 4, 6, and 8, the	Primary: The SVR12 was achieved in 90% of treatment-naïve and 86% in treatment-experienced patient, with an overall SVR12 rate of 89%. Secondary: The proportion of patients achieving HCV-RNA levels <LLOQ, detectable or undetectable, at early on-treatment time points in the treatment-naïve and treatment-experienced cohorts, respectively, was 40% and 24% for week one, 77% and 69% for week two, and 94% and 98% for week four. HCV-RNA levels were undetectable at end of treatment in 99% of patients. The SVR12 was 92% (55/60) and 87% (80/92) in patients with CC and non-CC IL28B genotype, respectively. SVR12 rates were higher in patients without cirrhosis (96% [105/109]) than

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	such as inhibitors of cyclophilin or microRNA) with baseline HCV-RNA levels ≥10,000 IU/mL Patients were excluded if they previously received treatment with NS5A inhibitor or discontinued treatment with sofosbuvir plus ribavirin prematurely because of intolerance (other than exacerbation of anemia)		end of treatment, and post-treatment weeks 4 and 24; and SVR12 rates by baseline cirrhosis status and IL28B genotype	in patients with cirrhosis (63% [20/32]).

Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel group, R=randomized, RCT=randomized control trial, SG=single-group
Miscellaneous abbreviations: HCV=hepatitis C virus, LLOQ=lower limit of quantification, PEG=peginterferon, RBV=ribavirin, RNA=ribonucleic acid, SVR=sustained virologic response, SVR12=sustained virologic response at 12 weeks after post- therapy, SVR24= sustained virologic response at 24 weeks post-therapy

Special Populations

Table 5. Special Populations[1-7]

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Daclatasvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	No data in pregnant women are available.*	Unknown; use with caution
Simeprevir	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required in mild impairment; safety and efficacy in moderate to severe hepatic impaired have not been established.	C*	Unknown; use with caution.
Sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been established in severe renal impairment (eGFR <30 mL/ min) or hemodialysis; no dose recommendation can be given.	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated cirrhosis.	B*	Unknown; use with caution.
Combination Products					
Ledipasvir/ sofosbuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the	No dosage adjustment required in mild or moderate renal impairment. Safety and efficacy have not been	No dosage adjustment required. Safety and efficacy have not been established in patients with decompensated	B	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	elderly. Safety and efficacy in children <18 years of age have not been established.	established in severe renal impairment (eGFR <30 mL/ minute) or ESRD requiring hemodialysis; no dose recommendation can be given.	cirrhosis.		
Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. No dosage adjustment required in the elderly. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required in mild, moderate or severe renal impairment.	No dosage adjustment required in mild hepatic impairment (Child-Pugh A). Not recommended in moderate hepatic impairment (Child-Pugh B). Contraindicated in severe hepatic impairment (Child-Pugh C).	B*	Unknown; use with caution.
Ombitasvir/ paritaprevir/ ritonavir/	Clinical studies did not include sufficient numbers of elder patients to assess safety or efficacy. No dosage adjustment is required in elderly patients. Safety and efficacy in children <18 years of age have not been established.	No dosage adjustment required. Safety and efficacy have not been established in patients on dialysis.	No dosage adjustment required in mild hepatic impairment (Child-Pugh A). Safety has not been established in moderate hepatic impairment (Child-Pugh B); use is not recommended. Contraindicated in severe hepatic impairment (Child-Pugh C).	B*	Unknown; use with caution.

eGFR=estimated glomerular filtration rate, ESRD=end stage renal disease
*Ribavirin has a pregnancy category of X. The use of any direct acting hepatitis C antiviral regimen containing ribavirin is contraindicated in pregnancy.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-7]

Adverse Event(s)	Daclatasvir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir‖	Ombitasvir/ paritaprevir/ ritonavir¶
Alopecia	-	-	-	-	-	-
Anemia	-	-	6§ to 21†	-	-	-
Arthralgia	-	-	-	-	-	-
Asthenia	-	-	5† to 21§	-	4/9	25/29
Chills	-	-	2§,‡ to 17†	-	-	-
Decreased appetite	-	-	6*‡ to 18†	-	-	-
Diarrhea	5	-	9‡ to 12§,†	3 to 7	-	-
Dizziness	-	-	-	-	-	-
Dry mouth	-	-	-	-	-	-
Dry skin	-	-	-	-	-	-
Dysgeusia	-	-	-	-	-	-
Dyspnea	-	12	-	-	-	-
Fatigue	14	-	30* to 59†	13 to 18	-	7/15
Headache	14	-	24‡ to 36†	11 to 17	-	-
Influenza like illness	-	-	3‡ to 16†	-	-	-
Insomnia	-	-	15‡ to 25†	3 to 6	5/12	5/13
Irritability	-	-	10*,‡ to 13†	-	-	-
Myalgia	-	16	6‡ to 14†	-	-	-
Nausea	8-	22	13* to 34†	6 to 9	8/16	9/14
Neutropenia	-	-	<1*,‡ to 17†	-	-	-
Pruritus	-	22	11‡ to 27*	-	7/13	5/7
Pyrexia	-	-	4*,‡ to 18†	-	-	-
Rash		28	8‡ to 18†	-	-	-
Skin reaction	-	-	-	-	-	5/7
Vomiting		-	-	-	-	-

-Incidence not reported or <1%
*Reported as: treatment-naïve patients/previous treatment failures (percent/percent).
†Sofosbuvir plus peginterferon alfa and weight-based ribavirin for 12 weeks treatment regimen.
‡Sofosbuvir plus weight-based ribavirin for 12 weeks treatment regimen.
§Sofosbuvir plus weight-based ribavirin for 24 weeks treatment regimen.
‖Reported as: (ombitasvir/paritaprevir/ritonavir/dasabuvir)/(ombitasvir/paritaprevir/ritonavir/dasabuvir + ribavirin)
¶Reported as: (ombitasvir/paritaprevir/ritonavir)/(ombitasvir/paritaprevir/ritonavir + ribavirin)

Contraindications

When direct acting hepatitis C antivirals are used in combination with pegylated interferon alfa and/or ribavirin, contraindications to those agents also apply to the direct acting hepatitis C antivirals. Ribavirin may cause birth defects and/or death of the exposed fetus and is contraindicated in pregnancy.[1-6] Refer to individual label information for pegylated interferon alfa and ribavirin for contraindications associated with those agents.[27-35]

Table 7. Contraindications[1-6]

Contraindications	Daclatasvir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Ombitasvir/ paritaprevir/ ritonavir
Coadministration with drugs that are highly dependent on cytochrome P450 (CYP) 3A for clearance					a	a
Coadministration with drugs that strongly induce CYP2C8					a	
Coadministration with drugs that strongly induce CYP3A	a				a	a
Coadministration with drugs that strongly inhibit CYP2C8					a	
Coadministration with drugs that moderately induce CYP3A						a
Hepatic impairment, severe					a	a
Hypersensitivity to the drug or any component	a	a	a	a	a	a

Warnings/Precautions

Table 8. Warnings/Precautions[1-6]

Warnings/Precautions	Daclatasvir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Ombitasvir/ paritaprevir/ ritonavir
Alanine transaminase (ALT) increases to five times the upper limit has been reported in 1% of patients; significantly more frequent in females ethinyl estradiol-containing medications					a	a
Certain drug interactions may lead to loss of therapeutic effect and should be discontinued.						a
Embryofetal toxicity (use with ribavirin and peginterferon alfa)	a	a	a		a	
HCV/HIV co-infected patients should also be on a suppressive antiretroviral drug regimen to reduce the risk of HIV protease inhibitor drug resistance.						a
Hypersensitivity reactions, severe/acute (with ribavirin/peginterferon)						
Monotherapy not recommended; must be used in	a	a	a			

Warnings/Precautions	Daclatasvir	Simeprevir	Sofosbuvir	Ledipasvir/ sofosbuvir	Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Ombitasvir/ paritaprevir/ ritonavir
combination therapy						
P-gp inducers (potent) reduce therapeutic effect			a	a		
Photosensitivity reactions have been reported (with ribavirin/peginterferon)		a				
Rash has been reported (use with ribavirin and peginterferon alfa)		a				
Symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with another daclatasvir.	a					

When used in combination with peginterferon alfa or ribavirin the warnings and associated with those agents are also applicable to the hepatitis C direct acting antivirals. Refer to the individual labels for these agents for a complete list of warnings and precautions associated with them. [27-35] The Black Box Warnings for those agents are outlined below.

Black Box Warning for peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (Peg Intron®, Sylatron®)[36-38]

WARNING
Alfa interferons, including peginterferon alfa-2a and alfa-2b, may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping peginterferon alfa-2a or alfa-2b therapy. Use with ribavirin: ribavirin may cause birth defects and/or death of the fetus. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease.

,

Black Box Warnings for ribavirin (Copegus®, Moderiba®, Moderiba Pak®, Rebetol®, Ribasphere®, Ribasphere RibaPak® and Ribatab®)[39-42]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions. Patients with a history of significant or unstable cardiac disease should not be treated with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple dose half-life of 12 days, and it may persist in non-plasma compartments for as long as six months. Therefore, ribavirin is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for six months after completion of therapy in both female patients and in female partners of male patients who are taking ribavirin therapy. At least two reliable forms of effective contraception must be utilized during treatment and during the six month post treatment follow up period.

Drug Interactions

Table 9a. Drug Interactions – Single-Entity Products (Not All Inclusive)[1-3]

Generic Name	Interacting Medication or Disease	Potential Result
Hepatitis C protease inhibitors (all)	Barbiturates	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	HMG-CoA Reductase Inhibitors	HMG-CoA Reductase Inhibitors plasma concentrations may be elevated, increasing the pharmacologic effects and risk of myopathy and rhabdomyolysis. Coadministration of boceprevir or telaprevir with either lovastatin or simvastatin is contraindicated. Coadministration of atorvastatin with telaprevir is contraindicated. Atorvastatin dose should not exceed 40 mg daily when coadministered with either boceprevir or simeprevir. Rosuvastatin dose should not exceed 10 mg daily when coadministered with

Generic Name	Interacting Medication or Disease	Potential Result
		simeprevir.
Hepatitis C protease inhibitors (all)	Human Immunodeficiency Virus Protease Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Human Immunodeficiency Virus Protease Inhibitors. Co-administration of simeprevir with any Human Immunodeficiency Virus Protease Inhibitor, with or without ritonavir, is not recommended. Co-administration of boceprevir or telaprevir with either darunavir/ritonavir or lopinavir/ritonavir is not recommended. Co-administration of boceprevir with atazanavir/ritonavir is not recommended. Co-administration of telaprevir with fosamprenavir/ritonavir is not recommended.
Hepatitis C protease inhibitors (all)	Hydantoins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Hydantoin concentrations may be elevated or reduced.
Hepatitis C protease inhibitors (all)	Non-Nucleoside Reverse Transcriptase Inhibitors	Hepatitis C protease inhibitor plasma concentrations may be altered by certain Non-Nucleoside Reverse Transcriptase Inhibitors. Co-administration of boceprevir or simeprevir with efavirenz is not recommended. Telaprevir dosage should be increased to 1,125 mg every eight hours when co-administered with efavirenz. Co-administration of any Hepatitis C protease inhibitor with nevirapine is not recommended. Co-administration of simeprevir with delavirdine or etravirine is not recommended.
Hepatitis C protease inhibitors (all)	Rifamycins	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Rifamycin concentrations may be elevated by boceprevir or telaprevir, increasing the risk of adverse reactions.
Hepatitis C protease inhibitors (all)	Carbamazepine	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response.
Hepatitis C protease inhibitors (all)	Cisapride	Cisapride plasma concentrations may be elevated, increasing the pharmacologic effects and risk of cardiac arrhythmias.
Hepatitis C protease inhibitors (all)	St. John's Wort	Hepatitis C protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response
Daclatasvir	Strong CYP3A4 inhibitors	Increased concentration of daclatasvir. Decrease dose to 30 mg once daily if coadministered with a strong CYP3A4 inhibitor.
Daclatasvir	Moderate CYP3A inhibitors	Increased concentration of daclatasvir. Monitor for increased side effects.
Daclatasvir	Moderate CYP3A inducers	Decreased concentration of daclatasvir. Increase dose to 90 mg once daily if coadministered with a strong CYP3A4 inhibitor.
Daclatasvir	Dabigatran etexilate mesylate	Co-administration is not recommended in severe renal impairment (creatinine clearance 15 to 30 mL/min). In patients being treated for recurrent deep vein thrombosis and pulmonary embolism, avoid concomitant use in patients with creatinine clearance <50 mL/min.
Daclatasvir	Amiodarone	Coadministration with amiodarone and sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. If coadministration is required, cardiac monitoring is recommended.
Daclatasvir	Digoxin	Increased concentration of digoxin. *Patients on daclatasvir initiating digoxin:* Use the lowest dosage of digoxin, monitor digoxin

Generic Name	Interacting Medication or Disease	Potential Result
		concentrations, and adjust digoxin doses, if necessary. *Patients on digoxin prior to initiating daclatasvir:* Measure digoxin concentrations before initiating daclatasvir, decrease digoxin dosage by approximately 30 to 50% or by modifying the dosing frequency and continue monitoring.
Daclatasvir	HMG-CoA reductase inhibitors	Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy.
Simeprevir	Antifungals	Simeprevir plasma concentrations may be increased by certain antifungals. Co-administration with systemic itraconazole, fluconazole, ketoconazole, posaconazole, and voriconazole is not recommended.
Simeprevir	Clarithromycin, erythromycin, telithromycin	Simeprevir plasma concentrations may be increased. Erythromycin plasma concentration may also be increased. Co-administration with clarithromycin, erythromycin or telithromycin is not recommended.
Simeprevir	Dexamethasone	Simeprevir plasma concentrations may be reduced by systemic dexamethasone. Co-administration with systemic dexamethasone is not recommended.
Simeprevir	Elvitegravir/cobicistat/ emtricitabine/tenofovir	Simeprevir plasma concentrations may be increased by cobicistat-containing product elvitegravir/cobicistat/emtricitabine /tenofovir. Co-administration with cobicistat-containing product is not recommended. □
Simeprevir	Oxcarbazepine	Simeprevir plasma concentrations may be reduced, leading to loss of virologic response.

Table 9b. Drug Interactions – Polymerase Inhibitors (Not All Inclusive)[3,4,6]

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir	Antacids: aluminum and magnesium hydroxide	Coadministration may result in decreased plasma concentrations of ledipasvir. It is recommended to separate antacid and ledipasvir/sofosbuvir administration by four hours.
Ledipasvir	H_2-receptor antagonists: famotidine	H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from ledipasvir/sofosbuvir at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
Ledipasvir	Proton-pump inhibitors: omeprazole	Proton-pump inhibitor doses comparable to omeprazole 20 mg or lower can be administered simultaneously with ledipasvir/sofosbuvir under fasted conditions.
Ledipasvir	Antiarrhythmics: digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Ledipasvir, Sofosbuvir	Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to loss of therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	Rifampin, rifabutin, rifapentine	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.
Ledipasvir, Sofosbuvir	St. John's wort (*Hypericum perforatum*)	Coadministration may result in decreased plasma concentrations of sofosbuvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Generic Name	Interacting Medication or Disease	Potential Result
Ledipasvir, Sofosbuvir	Tipranavir/ritonavir	Coadministration may result in decreased plasma concentrations of sofosbuvir and/or ledipasvir leading to reduced therapeutic effect of sofosbuvir. Coadministration is not recommended.

Table 9c. Drug Interactions Ombitasvir/Paritaprevir/Ritonavir/Dasabuvir - (Not All Inclusive)[5,6]

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Alfuzosin	Increased alfuzosin concentration, increased risk for hypotension; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Anticonvulsants (carbamazepine, phenytoin, phenobarbital)	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Gemfibrozil	Increased concentration of dasabuvir (10x); increased risk of QT prolongation; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rifampin	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)	Increased ergot derivative concentrations; acute ergot toxicity characterized by vasospasm and tissue ischemia; contraindicated.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	St. John's Wort	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (lovastatin, simvastatin)	Increased concentrations of lovastatin and simvastatin; potential for myopathy; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Efavirenz	Coadministration was poorly tolerated and resulted in liver enzyme elevations.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sildenafil	Increased concentrations of sildenafil; potential for visual disturbances, hypotension, priapism and syncope; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sedatives/hypnotics (triazolam midazolam [oral])	Coadministration may cause large increases in benzodiazepine concentration. The potential exists for serious and/or life threatening events such as sedation or respiratory depression; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine, mexiletine, propafenone, quinidine)	Decreased concentration of antiarrhythmics; caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ketoconazole	Increased ketoconazole concentration; limit max daily dose of ketoconazole to 200 mg per day
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Voriconazole	Decreased voriconazole concentration; coadministration not recommended (benefit-to-risk justifies use)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Amlodipine	increased concentration of amlodipine; dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Fluticasone	Increased fluticasone concentration; may alter cortisol levels; use an alternate corticosteroid
Ombitasvir/paritaprevir/	Furosemide	Furosemide concentration increased, dose adjust

Generic Name	Interacting Medication	Potential Result
ritonavir/dasabuvir		
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Atazanavir/ritonavir, lopinavir/ritonavir	Increased concentrations of paritaprevir; only coadminister atazanavir without ritonavir and limit to 300 mg in the morning; do not coadminister lopinavir/ritonavir
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Darunavir/ritonavir	Decreased concentration of darunavir; coadministration is not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rilpivirine	Increased concentration of rilpivirine; increased risk of QT interval prolongation
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (rosuvastatin, pravastatin)	Increased concentrations of the statins; limit dose to 10 mg (rosuvastatin) and 40 mg (pravastatin)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Cyclosporine	Increased concentration of cyclosporin; when coadministered, reduce cyclosporine dose to 1/5th of the current dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Tacrolimus	Increased concentration of tacrolimus; when coadministered, reduce tacrolimus dose. Measure tacrolimus blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and tacrolimus-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Salmeterol	Increased concentration of salmeterol; increased risk of cardiovascular event; coadministration not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Buprenorphine (±naloxone)	Increased concentration of buprenorphine; no dose adjustment required; monitor for adverse effects
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Omeprazole	Decreased concentration of omeprazole; limit dose to 40 mg or less
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Alprazolam	increased concentration of alprazolam; monitor for side effects; dose adjust based on clinical response

Table 9d: ombitasvir/paritaprevir/ritonavir- (Not All Inclusive)[6]

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir	Alfuzosin	Potential for hypotension; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Anticonvulsants: carbamazepine, phenytoin, phenobarbital	Loss of therapeutic activity of HCV regimen; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Ergot derivatives	Acute ergot toxicity characterized by vasospasm and tissue ischemia; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Ethinyl estradiol-containing products	Potential for ALT elevations; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	St. John's Wort	Loss of therapeutic activity of HCV regimen; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	HMG-CoA reductase inhibitors: lovastatin, simvastatin	Potential for myopathy; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Neuroleptics	Potential for cardiac arrhythmias. contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Efavirenz	Coadministration was poorly tolerated and resulted in liver enzyme elevations.

Generic Name	Interacting Medication	Potential Result
Ombitasvir/paritaprevir/ ritonavir	Sildenafil	Potential for visual disturbances, hypotension, priapism and syncope; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Sedatives/hypnotics: triazolam, midazolam (oral)	Coadministration may cause large increases in benzodiazepine concentration. The potential exists for serious and/or life threatening events such as sedation or respiratory depression; contraindicated.
Ombitasvir/paritaprevir/ ritonavir	Digoxin	Decrease digoxin dose by 30-50%. Appropriate monitoring of serum digoxin levels is recommended.
Ombitasvir/paritaprevir/ ritonavir	Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring (if available) is recommended for antiarrhythmics when coadministered.
Ombitasvir/paritaprevir/ ritonavir	Ketoconazole	When co-administered with ketoconazole, the maximum daily dose of ketoconazole should be limited to 200 mg/day.
Ombitasvir/paritaprevir/ ritonavir	Voriconazole	Coadministration with voriconazole is not recommended unless the benefit-to-risk ratio justifies use.
Ombitasvir/paritaprevir/ ritonavir	Quetiapine	Stable on quetiapine: consider alternative anti-HCV therapy. Initiating quetiapine: refer do quetiapine prescribing information for initial dosing and titration.
Ombitasvir/paritaprevir/ ritonavir	Amlodipine	Consider dose reduction for amlodipine. Clinical monitoring is recommended.
Ombitasvir/paritaprevir/ ritonavir	Fluticasone	Coadministration with inhaled or nasal fluticasone may reduce serum cortisol concentrations. Alternative corticosteroids should be considered, particularly for long-term use.
Ombitasvir/paritaprevir/ ritonavir	Furosemide	Clinical monitoring of patients is recommended and therapy should be individualized based on patient's response.
Ombitasvir/paritaprevir/ ritonavir	Atazanavir or Atazanavir/ritonavir Lopinavir/ritonavir	Coadministration is not recommended, increased concentration of paritaprevir
Ombitasvir/paritaprevir/ ritonavir	Darunavir/ritonavir	Technivie® (ombitasvir/paritaprevir/ritonavir) and darunavir 800 mg (without ritonavir) should be taken at the same time.
Ombitasvir/paritaprevir/ ritonavir	rilpivirine	Coadministration with rilpivirine daily is not recommended due to potential for QT interval prolongation.
Ombitasvir/paritaprevir/ ritonavir	pravastatin	When coadministered with pravastatin, the dose of pravastatin should not exceed 40 mg per day.
Ombitasvir/paritaprevir/ ritonavir	cyclosporine	When coadministered, reduce cyclosporine dose to 1/5th of the current dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir	tacrolimus	When coadministered, reduce tacrolimus dose. Measure tacrolimus blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and tacrolimus-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir	salmeterol	Coadministration with salmeterol is not recommended due to increased risk of cardiovascular events, including QT prolongation, palpitations and sinus tachycardia.
Ombitasvir/paritaprevir/ ritonavir	buprenorphine	When coadministered, no dose adjustment of buprenorphine/naloxone is required. Patients should be

Generic Name	Interacting Medication	Potential Result
		monitored for sedation and cognitive effects.
Ombitasvir/paritaprevir/ ritonavir	omeprazole	Monitor patients for decreased efficacy of omeprazole. Avoid use of more than 40 mg/day.
Ombitasvir/paritaprevir/ ritonavir	alprazolam	Clinical monitoring is recommended. A decrease in alprazolam dose can be considered based on clinical response.

HCV=Hepatitis C Virus

Dosage and Administration

Table 10. Dosing and Administration[1-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Daclatasvir	Treatment of chronic HCV genotype 3 in combination with sofosbuvir (no cirrhosis): Tablet: 60 mg QD with or without food for 12 weeks in combination with sofosbuvir. Decrease dose to 30 mg QD when coadministered with strong CYP3A inhibitors. Increase dosing to 90 mg QD when coadministered with moderate CYP3A inducers.	Safety and efficacy in children have not been established.	Tablet: 30 mg 60 mg
Simeprevir	Treatment on chronic hepatitis C genotype 1 infection as a component of a combination antiviral treatment regimen with peginterferon alfa plus ribavirin: Capsule: 150 mg QD with food for 12 weeks Treatment on chronic hepatitis C genotype 1 infection as a component of a combination antiviral treatment regimen with sofosbuvir: Capsule: 150 mg QD with food for 12 or 24 weeks	Safety and efficacy in children have not been established.	Capsule: 150 mg
Sofosbuvir	Treatment of chronic HCV genotype 1 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin; treatment in combination with ribavirin alone (without peginterferon alfa) can be considered for hepatitis C patients with genotype 1 infection who are ineligible to receive an interferon-based regimen: Tablet: 400 mg QD for 12 weeks (with peginterferon alfa and ribavirin) or 24 weeks (with ribavirin alone in patients ineligible to receive an interferon-based regimen) Treatment of chronic HCV genotype 4 infection, including HCV/HIV-1 co-infection, in combination with peginterferon alfa and ribavirin: Tablet: 400 mg QD for 12 weeks Treatment of chronic HCV genotype 2 or 3 infection, including HCV/HIV-1 co-infection, in combination with ribavirin: Tablet: 400 mg QD for 12 weeks (genotype 2) or 24 weeks (genotype 3) Prevention of post-transplant HCV reinfection in patients with	Safety and efficacy in children have not been established.	Tablet: 400 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation), including patients with HCV/HIV-1 co-infection: Tablet: 400 mg QD for up to 48 weeks or until liver transplantation, whichever occurs first		
Combination Products			
Ledipasvir/ sofosbuvir	Treatment of chronic HCV genotype 1 infection: Tablet: 90/400 mg QD for 12 weeks (treatment-naïve with or without cirrhosis* or treatment-experienced without cirrhosis) or 90/400 mg QD for 24 weeks (treatment-experienced with cirrhosis).	Safety and efficacy in children have not been established.	Tablet: 90/400 mg
Ombitasvir/ paritaprevir/ ritonavir/ dasabuvir	Treatment of genotype 1a chronic HCV infection without cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 12 weeks Treatment of genotype 1a chronic HCV infection with cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 24 weeks (12 weeks may be considered for some patients based on prior treatment history) Treatment of genotype 1b chronic HCV infection without cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID for 12 weeks Treatment of genotype 1b chronic HCV infection with cirrhosis Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet BID with ribavirin for 12 weeks Treatment of genotype 1 chronic HCV infection in liver transplant recipients with normal hepatic function and mild fibrosis (F2 or lower) Tablet: Two ombitasvir/paritaprevir/ritonavir 12.5/75/50 mg tablets QD and one dasabuvir 250 mg tablet twice daily with ribavirin for 24 weeks	Safety and efficacy in children have not been established.	Tablet: 12.5/75/50 mg (Ombitasvir/ paritaprevir/ ritonavir) 250 mg (Dasabuvir)
Ombitasvir/ paritaprevir/ ritonavir	Treatment of chronic HCV genotype 4 in combination with ribavirin, in patients without cirrhosis: Tablet: Two tablets QD (in the morning) with a meal without regard to fat or calorie content plus weight-based ribavirin for 12 weeks.†	Safety and efficacy have not been established.	Tablet: 12.5/75/50 mg

BID=twice daily, HCV=hepatitis C virus, HIV=human immunodeficiency virus, QD=once daily, TID=three times a day
*Ledipasvir/sofosbuvir may be considered for 8 weeks of therapy in treatment-naïve patients without cirrhosis who have pre-treatment HCV RNA less than 6 million IU/mL.
†Ombitasvir/paritaprevir/ritonavir may be considered for therapy without ribavirin may be considered for treatment-naïve patients who cannot take or tolerate ribavirin.

Table 11. Simeprevir Duration of Treatment[2]

	Recommendations		
	Triple Therapy (Simeprevir, Peginterferon alfa and Ribavirin)*	**Dual Therapy (Peginterferon alfa and Ribavirin)***	**Total Treatment Duration***
Treatment-Naïve and Prior Relapse Patients Including Those with Cirrhosis	First 12 weeks	Additional 12 weeks	24 weeks
Prior Partial and Null Responder Patients Including Those with Cirrhosis	First 12 weeks	Additional 36 weeks	48 weeks

*If the patient has hepatitis C virus (HCV) ribonucleic acid (RNA) results ≥25 IU/mL at treatment week four or 12, discontinue simeprevir, peginterferon alfa and ribavirin. If the patient has HCV RNA results ≥25 IU/mL at treatment week 24, then discontinue peginterferon alfa and ribavirin. In clinical trials, HCV RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25.0 IU/mL and a limit of detection of 15 IU/mL.

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2015)**[33]	Goal of treatment · The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). When and in whom to initiate treatment · Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies owing to comorbid conditions. · Immediate treatment is assigned the highest priority for those patients with the highest risk for severe complications. o Metavir F3 or Metavir F4 o Liver transplant recipients o Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (e.g., vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis · Based on available resources, immediate treatment should be prioritized as necessary so that patients at high risk for liver-related complications and severe extrahepatic hepatitis C complications are given high priority. o Fibrosis (Metavir F2) o HIV-1 coinfection o Hepatitis B virus (HBV) coinfection o Other coexistent liver disease (e.g., nonalcoholic steatohepatitis [NASH]) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda · Treatment of individuals at high risk to transmit HCV to others may yield long-term future benefits from decreased transmission and a potential decrease in HCV disease prevalence. o Men who have sex with men (MSM) with high-risk sexual practices o Active injection drug users o Incarcerated persons o Persons on long-term hemodialysis o HCV-infected women of child-bearing potential wishing to get pregnant o HCV-infected health care workers who perform exposure-prone

Clinical Guideline	Recommendation(s)
	procedures · An assessment of the degree of hepatic fibrosis, using noninvasive testing or liver biopsy, is recommended. · Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred. <u>Initial treatment of HCV infection (treatment-naïve)</u> · <u>Genotype 1a</u> (several options with similar efficacy are recommended) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks (no cirrhosis) or with or without weight-based ribavirin for 24 weeks (cirrhosis). Adjust daclatasvir dose with CYP3A4 inducers/inhibitors. o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg plus weight-based ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis without Q80K polymorphism) · <u>Genotype 1b</u> (several options with similar efficacy are recommended) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks (no cirrhosis) or with or without weight-based ribavirin for 24 weeks (cirrhosis). Adjust daclatasvir dose with CYP3A4 inducers/inhibitors. o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg for 12 weeks § The addition of weight-based ribavirin is recommended in patients with cirrhosis o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without ribavirin for 12 weeks (no cirrhosis) or 24 weeks (cirrhosis) · Shortening treatment to less than 12 weeks for patients without cirrhosis should be done with caution and performed at the discretion of the practitioner · The following regimens are <u>NOT recommended</u> for treatment-naïve patients with HCV genotype 1 o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Peginterferon alfa and ribavirin with or without sofosbuvir, simeprevir, telaprevir, or boceprevir for 12 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral · <u>Genotype 2</u> o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks for patients with ribavirin intolerance. Adjust daclatasvir dose CYP3A4 with inducers/inhibitors. o Daily sofosbuvir 400 mg and weight based ribavirin for 12 weeks § Extending treatment to 16 weeks is recommended in patients with cirrhosis · The following regimens are <u>NOT recommended</u> for treatment-naïve patients with HCV genotype 2 o Peginterferon alfa and ribavirin for 24 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or ledipasvir-containing regimens · <u>Genotype 3</u> o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks (cirrhosis) or with or without weight-based ribavirin for 24 weeks (cirrhosis). Adjust daclatasvir dose CYP3A4 with inducers/inhibitors. o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly

Clinical Guideline	Recommendation(s)
	peginterferon alfa for 12 weeks for interferon eligible patients o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks for interferon ineligible patients · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 3 o Peginterferon alfa and ribavirin for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral o Telaprevir-, boceprevir-, or ledipasvir-containing regimens · Genotype 4 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternate: § Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks § Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 4 o Peginterferon alfa and ribavirin with or without simeprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · Genotype 5 or 6 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for treatment-naïve patients with HCV genotype 5 or 6 o Peginterferon alfa and ribavirin with or without simeprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · Mixed Genotypes o Treatment data for mixed genotypes with direct-acting antivirals are sparse, and awaiting availability of a pangenotypic regimen may be considered. o When treatment is necessary, the choice of antiviral combination and duration of treatment should maximize efficacy against each genotype represented in the assay. Retreatment after failed therapy (peginterferon alfa and ribavirin) · Genotype 1a (no cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg plus simeprevir 150 mg for 12 weeks · Genotype 1b (no cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg for 12 weeks

Clinical Guideline	Recommendation(s)
	o Daily sofosbuvir 400 mg plus simeprevir 150 mg for 12 weeks · Genotype 1a or 1b (with cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 24 weeks with or without weight-based ribavirin o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg plus weight-based ribavirin for 12 weeks o Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice daily dasabuvir 250 mg and weight-based ribavirin for 24 weeks (genotype 1a) or 12 weeks without ribavirin (genotype 1b) o Daily sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 24 weeks (genotype 1b or 1a who are negative for Q80K variant); consider alternative regimens if Q80K variant is present. · Genotype 2 o Daily sofosbuvir 400 mg and weight-based ribavirin for 16 to 24 weeks; decision to extend treatment to 16 to 24 weeks should be made on an individual patient basis. o Alternate (peginterferon alfa eligible): Retreatment with daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for patients with HCV genotype 2 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin with or without telaprevir or boceprevir o Fixed-dose combination ledipasvir/sofosbuvir 90/400 mg o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · Genotype 3 o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks without ribavirin (no cirrhosis) or 24 weeks with weight-based ribavirin (cirrhotics ineligible for peginterferon alfa) o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks for interferon eligible patients o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks for interferon ineligible patients · The following regimens are NOT recommended for patients with HCV genotype 3 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin for 24 weeks to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or simeprevir-based regimens · Genotype 4 o Daily ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg and weight-based ribavirin for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin for 24 weeks · The following regimens are NOT recommended for patients with HCV genotype 4 who have failed peginterferon alfa and ribavirin o Peginterferon alfa and ribavirin with or without telaprevir or boceprevir o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral Retreatment after failed therapy (HCV protease inhibitor plus peginterferon alfa and ribavirin) · Genotype 1 (no cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks

Clinical Guideline	Recommendation(s)
	o Daily ledipasvir/sofosbuvir 90/400 mg with weight-based ribavirin for 12 weeks · Genotype 1 (cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg with or without weight-based ribavirin for 24 weeks. o Daily ledipasvir/sofosbuvir 90/400 mg with weight-based ribavirin for 12 weeks or without ribavirin for 24 weeks Retreatment after failed therapy (sofosbuvir plus simeprevir) · Genotype 1 (no cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg for 12 weeks o Daily ledipasvir/sofosbuvir 90/400 mg with weight-based ribavirin for 12 weeks · Genotype 1 (cirrhosis) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg with or without weight-based ribavirin for 24 weeks. o Daily ledipasvir/sofosbuvir 90/400 mg for 24 weeks · The following regimens are NOT recommended for patients with HCV genotype 1 who have failed an HCV protease inhibitor containing regimen o Any regimen containing peginterferon alfa, including: § Simeprevir, ribavirin and peginterferon alfa § Sofosbuvir, ribavirin and peginterferon alfa § Telaprevir or boceprevir, peginterferon alfa and ribavirin § Peginterferon alfa and ribavirin dual therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Any interferon-free regimen containing an HCV protease inhibitor § Simeprevir or paritaprevir Retreatment after failed therapy (HCV NS5A inhibitor, including daclatasvir plus sofosbuvir, ledipasvir/sofosbuvir and paritaprevir/ritonavir/ombitasvir plus dasabuvir) · Genotype 1 (no cirrhosis) o For patients with minimal liver disease, deferral of treatment is recommended, pending availability of data. · Genotype 1 (cirrhosis or other need for urgent treatment) o Testing for resistance associated variants (RAVs) that confer decreased susceptibility to NS3 protease inhibitors (e.g., Q80K) and to NS5A inhibitors should be performed using commercially available assays. o NS5A RAVs detected § Ledipasvir/sofosbuvir and ribavirin for 24 weeks o NS5A RAVs detected and no NS3 RAVs detected § Sofosbuvir plus simeprevir and ribavirin for 24 weeks o NS3 and NS5A RAVs detected § Retreat in clinical trial settings Retreatment after failed therapy (sofosbuvir plus ribavirin) · Genotype 2 o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Daily daclatasvir 60 mg plus sofosbuvir 400 mg with or without weight-based ribavirin for 24 weeks (interferon ineligible only) Retreatment after failed therapy (sofosbuvir plus ribavirin) · Genotype 3

Clinical Guideline	Recommendation(s)
	o Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks o Daily daclatasvir 60 mg plus sofosbuvir 400 mg with weight-based ribavirin for 24 weeks (interferon ineligible only) Retreatment after failed therapy (genotypes 5 and 6) · Few data are available to help guide decision making for patients infected with HCV genotype 5 or 6. · Recommendations for genotypes 5 and 6 do not specify which treatments have been failed previously. · Genotype 5 or 6 o Daily fixed-dose ledipasvir/sofosbuvir 90/400 mg for 12 weeks o Alternate: Daily sofosbuvir 400 mg and weight-based ribavirin plus weekly peginterferon alfa for 12 weeks · The following regimens are NOT recommended for patients with HCV genotypes 5 or 6 who have failed previous therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens Monitoring at onset, during treatment and after completion of HCV therapy · Recommended assessments prior to starting antiviral therapy o Assessment of potential drug-drug interactions o Laboratory tests within 12 weeks prior to starting: § Complete blood count (CBC); international normalized ratio (INR) § Hepatic function § Thyroid-stimulating hormone (TSH) (if interferon is used) § Calculated glomerular filtration rate (GFR) o Laboratory tests any time prior to starting: § HCV genotype and subtype § Quantitative HCV viral load, except in the circumstance that a quantitative viral load will influence duration of therapy · Monitoring during antiviral therapy o Routine monitoring for HCV drug resistance-associated variants during therapy is not recommended o Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications. o Laboratory § After four weeks of treatment or as clinically indicated: · CBC, creatinine level, calculated GFR, hepatic function § Every 12 weeks of treatment (for patients receiving interferon) · TSH o More frequent assessment for drug-related toxic effects (e.g., CBC for patients receiving ribavirin) is recommended as clinically indicated. o Prompt discontinuation of therapy is recommended for § A 10-fold increase in alanine aminotransferase (ALT) activity at week four § Any increase in ALT of less than 10-fold at week 4 that is accompanied by any weakness, nausea, vomiting, or jaundice, or accompanied by increased bilirubin, alkaline phosphatase, or INR. Asymptomatic increases in ALT of less than 10-fold elevated at week four should be closely monitored and repeated at week six and week eight.

Clinical Guideline	Recommendation(s)
	o Quantitative HCV viral load testing is recommended after 4 weeks of therapy and at 12 weeks following completion of therapy. § Antiviral therapy should NOT be interrupted or discontinued if HCV RNA levels are not performed or available during treatment. o Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy. · Recommendations for discontinuation of treatment due to lack of efficacy o HCV viral load is detectable at week four, repeat quantitative HCV viral load after two additional weeks of treatment (treatment week six). § If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or thereafter), discontinue HCV treatment. o The significance of a positive HCV RNA test result at week 4 that remains positive, but lower, at week six or week eight is unknown. § No recommendation to stop therapy or extend therapy can be provided at this time. · Recommended monitoring in patients who have failed to achieve a sustained virologic response: o Disease progression assessment every six to 12 months with a hepatic function panel, CBC, and INR is recommended. o Surveillance for hepatocellular carcinoma with ultrasound testing every six months is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4). o Endoscopic surveillance for esophageal varices is recommended if cirrhosis is present. o Evaluation for retreatment is recommended as effective alternative treatments become available. · Recommended follow-up for patients who achieve a sustained virologic response o For patients who do not have advanced fibrosis (i.e., those with Metavir stage F0-F2), recommended follow-up is the same as if they were never infected with HCV. o Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV RNA assay rather than an anti-HCV serology test is recommended to test for HCV recurrence or reinfection. o Surveillance for hepatocellular carcinoma with twice-yearly ultrasound testing is recommended for patients with advanced fibrosis (i.e., Metavir stage F3 or F4) who achieve an SVR. o A baseline endoscopy is recommended to screen for varices if cirrhosis is present. Patients in whom varices are found should be treated and followed up as indicated. o Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving an SVR. · Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and who are receiving immunosuppressive treatments (systemic corticosteroids, antimetabolites, chemotherapy, etc.) is NOT routinely recommended Special populations – pregnancy: · Monitoring for pregnancy-related issues prior to and during antiviral therapy (treatment includes ribavirin) o Women of childbearing age should be cautioned not to become pregnant

Clinical Guideline	Recommendation(s)
	while receiving RBV-containing antiviral regimens, and for up to six months after stopping. o Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin. o Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for six months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment. · The following regimens are NOT recommended with regard to pregnancy-related issues o Treatment is NOT recommended for pregnant women or for women who are unwilling to adhere to use of adequate contraception, including those who are receiving ribavirin themselves or are sexual partners of male patients who are receiving ribavirin. o Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should not become pregnant for at least 6 months after stopping ribavirin. Special populations – human immunodeficiency virus (HIV)/HCV coinfection · HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications. · The following regimens are NOT recommended for treatment-naïve or treatment-experienced HIV/HCV-coinfected patients o Peginterferon alfa and ribavirin with or without simeprevir, telaprevir or boceprevir for 24 to 48 weeks o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral · When switching antiviral drugs as needed for drug interactions between HIV and HCV antivirals, consult an HIV practitioner. o For the HIV antiretroviral and HCV direct-acting antiviral combinations not addressed below, expert consultation is recommended. · For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended · Ledipasvir/sofosbuvir o Ledipasvir increases tenofovir levels, creatinine clearance (CrCl) should be considered. § Avoid ledipasvir if CrCl <60 mL/min. § Avoid if tenofovir is boosted by ritonavir (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high. · Paritaprevir/ritonavir/ombitasvir/dasabuvir o Use with antiretroviral drugs with no substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine and atazanavir o The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with this combination and then restarted when HCV treatment is completed. § Administer the HIV protease inhibitor at the same time as the fixed-dose HCV combination. · Simeprevir o Only use with antiretrovirals with which it does not have clinically significant interactions: raltegravir (and probably dolutegravir), rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine and abacavir · The following are NOT recommended or should not be used:

Clinical Guideline	Recommendation(s)
	o Antiretroviral treatment interruption to allow HCV therapy o Ledipasvir/sofosbuvir with cobicistat and elvitegravir o Sofosbuvir or ledipasvir/sofosbuvir with 40iscontinu o Paritaprevir/ritonavir/ombitasvir/dasabuvir with efavirenz, rilpivirine, darunavir or ritonavir-boosted lopinavir o Paritaprevir/ritonavir/ombitasvir/dasabuvir should not be used in HIV/HCV-coinfected patients who are not taking antiretroviral therapy o Simeprevir with efavirenz, etravirine, nevirapine, cobicistat or any HIV protease inhibitors o Ribavirin with didanosine, stavudine or zidovudine <u>Special populations – decompensated cirrhosis</u> · Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). o The following regimens should only be used by highly experienced HCV practitioners. · <u>Genotype 1 or 4</u> (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma); o Daily daclatasvir 60 mg plus sofosbuvir 400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Daily ledipasvir/sofosbuvir 90/400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Alternate (ribavirin intolerant or ineligible): daclatasvir 60 mg plus sofosbuvir 400 mg for 24 weeks o Alternate (prior failure with a sofosbuvir-based regimen): Daily ledipasvir/sofosbuvir 90/400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 24 weeks · <u>Genotype 2 or 3</u> (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma) o Daily daclatasvir 60 mg plus sofosbuvir 400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Daily sofosbuvir 400 mg and weight-based ribavirin (with consideration of the patient's CrCl and hemoglobin level) for up to 48 weeks · The following regimens are <u>NOT recommended</u> for patients with decompensated cirrhosis: o Any interferon-based therapy o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir-, boceprevir-, or simeprevir-based regimens o Paritaprevir-, ombitasvir-, or dasabuvir-based regimens <u>Special populations – recurrent HCV infection post-liver transplantation</u> · <u>Genotype 1 or 4</u> infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily daclatasvir 60 mg plus sofosbuvir 400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Daily ledipasvir/sofosbuvir 90/400 mg with weight-based ribavirin for 12 weeks o Alternative (ribavirin intolerant or ineligible): daclatasvir 60 mg plus sofosbuvir 400 mg for 24 weeks o Alternative (ribavirin intolerant or ineligible): ledipasvir/sofosbuvir 90/400 mg for 24 weeks o Alternative (genotype 1 only): sofosbuvir 400 mg plus simeprevir 150 mg with or without weight-based ribavirin for 12 weeks

Clinical Guideline	Recommendation(s)
	o Alternative (genotype 1, including early [Metavir fibrosis stage F0-F2] recurrence): Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg and weight-based ribavirin for 24 weeks · Genotype 1 or 4 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Daily ledipasvir/sofosbuvir 90/400 mg with a low initial dose of ribavirin (600 mg, increasing as tolerated) for 12 weeks · Genotype 2 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily daclatasvir 60 mg plus sofosbuvir 400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Daily sofosbuvir 400 mg plus weight-based ribavirin for 24 weeks o Alternative (ribavirin intolerant or ineligible): daclatasvir 60 mg plus sofosbuvir 400 mg for 24 weeks · Genotype 2 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Daily sofosbuvir 400 mg with a low initial dose of ribavirin (600 mg, increased monthly by 200 mg/day as tolerated to a weight-based dose) for 24 weeks · Genotype 3 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daily daclatasvir 60 mg plus sofosbuvir 400 mg and ribavirin (initial dose 600 mg, increased as tolerated) for 12 weeks o Sofosbuvir 400 mg and weight-based ribavirin for 24 weeks o Alternative (treatment-naïve, ribavirin intolerant or ineligible): daclatasvir 60 mg plus sofosbuvir 400 mg for 24 weeks · Genotype 3 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir 400 mg and low initial dose of ribavirin (600 mg, increasing as tolerated) for 24 weeks · The following regimens are NOT recommended for treatment-naïve patients with compensated allograft HCV infection o Regimens containing peginterferon alfa o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens · The following regimens are NOT recommended for treatment-naïve patients with decompensated allograft HCV infection o Regimens containing peginterferon alfa o Regimens containing simeprevir o Daily paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg and weight-based ribavirin o Monotherapy with peginterferon alfa, ribavirin or a direct-acting antiviral o Telaprevir- or boceprevir-based regimens Special populations – renal impairment · Mild to moderate renal impairment (CrCl >30 mL/min) o Daclatasvir: no dosage adjustment is required o Sofosbuvir: no dosage adjustment is required o Simeprevir: no dosage adjustment is required o Ledipasvir/sofosbuvir: no dosage adjustment is required o Paritaprevir/ritonavir/ombitasvir and dasabuvir: no dosage adjustment is required · For CrCl<30 mL/min who do not have cirrhosis but for whom the urgency to treat (or retreat) is high and renal transplant is not an immediate option

Clinical Guideline	Recommendation(s)
	o HCV genotype 1b or 4 infection: Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg (genotype 1b) or without dasabuvir (genotype 4) o HCV genotype 1a infection: Daily fixed-dose paritaprevir/ritonavir/ombitasvir 150/100/25 mg plus twice-daily dasabuvir 250 mg (plus ribavirin if hemoglobin >10 g/dL at a dose of 200 mg trice weekly to daily) o HCV genotype 2, 3, 5, or 6 infection: peginterferon alfa and dose adjusted ribavirin if treatment is necessary and transplantation cannot be performed o Sofosbuvir-containing regimens can be considered after consultation with an expert, because safety and efficacy data are not available for these patients Management of acute HCV infection · HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels · Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended. · Medical management and monitoring o Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (every four to eight weeks) for six to 12 months is recommended to determine spontaneous clearance of HCV infection versus persistence of infection. o Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs and alcohol consumption, and to reduce the risk of HCV transmission to others. o Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use. · Treatment for patients with acute HCV infection o If treatment is delayed, monitoring for spontaneous clearance is recommended for a minimum of six months. o If treatment is to begin during the acute infection period, monitor HCV RNA for at least 12 to 16 weeks before starting treatment to allow for spontaneous clearance. o Treatment with the same standard regimens is recommended for chronic and acute HCV infection o Treatment is NOT recommended if HCV spontaneously clears.
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2015)**[34]	Goal of treatment · The goal of hepatitis C antiviral treatment is to achieve a sustained virological response (SVR), defined as undetectable HCV RNA in the blood 12 or more weeks after completing antiviral treatment. Principles for patient selection for HCV treatment · The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. · Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma (HCC) awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months. · Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short term, but should be informed of new treatments and their

Clinical Guideline	Recommendation(s)
	potential to cure HCV. · Patients with severe mental health conditions who are engaged in treatment or those with ongoing substance use including drinking alcohol, using illicit drugs, including marijuana, or participating in opioid replacement programs should not be excluded from HCV treatment. · Treatment is not indicated in patients with limited life expectancy (i.e., multiple comorbidities, non-curative hepatocellular cancer) unless there is reason to anticipate that duration or quality of life can be improved by eradication of HCV. · Factors that may complicate adherence, such as active substance abuse, depression, neurocognitive disorders, and lack of social support, should be addressed before initiating medications. Pre-treatment evaluation · HCV genotype, including subtype · HCV RNA (quantitative viral load) preferably within the past six months · Clinical assessment for cirrhosis · If cirrhotic, exclusion of hepatocellular carcinoma based on appropriate imaging study within the prior six months · Previous HCV treatment history and outcome · HIV status and, if HIV seropositive, current antiretroviral regimen and degree of viral suppression · Documented use of two forms of birth control in patient and sex partners in whom a ribavirin-containing regimen is chosen Treatment of HCV genotype 1 in treatment-naïve patients without cirrhosis · Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 12 weeks OR 8 weeks if baseline HCV RNA <6 million IU/mL. · Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; genotype (GT)1a: add ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses), GT1b: ribavirin not required. Treatment of HCV genotype 1 in treatment-naïve patients with cirrhosis · Child-Turcotte-Pugh A o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily with or without ribavirin for 12 weeks. o Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks; may consider 24 weeks for GT1a. · Child-Turcotte-Pugh B and C o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (600 mg/day with food, and increase by 200 mg/day every 2 weeks only as tolerated if hemoglobin remains above 10 g/dL) for 12 weeks. NOT FDA APPROVED. Treatment of HCV genotype 1 in treatment-experienced patients without cirrhosis (prior peginterferon/ribavirin experienced only) · Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 12 weeks. · Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) for 12 weeks; GT1a: add ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses), GT1b: ribavirin not

Clinical Guideline	Recommendation(s)
	required. Treatment of HCV genotype 1 in treatment-experienced patients with cirrhosis (prior peginterferon/ribavirin experienced only) · Child-Turcotte-Pugh A o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 24 weeks. o Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + dasabuvir (250 mg): 1 tablet twice daily (in the morning and in the evening with food) + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks if GT1a prior relapser or partial responder (may consider 24 weeks) or 24 weeks if GT1a null responder; 12 weeks if GT1b. · Child-Turcotte-Pugh (CTP) B and C o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (600 mg/day with food and increase by 200 mg/day every 2 weeks only as tolerated if hemoglobin remains above 10 g/dL) for 12 weeks. NOT FDA APPROVED. Treatment of HCV genotype 1 in treatment-naïve or experienced patients, with or without cirrhosis (prior DAA experienced) · Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. Treatment of HCV genotype 2 in treatment-naïve patients without cirrhosis · Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. Treatment of HCV genotype 2 in treatment-naïve patients with cirrhosis · Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 16 weeks. FDA APPROVED FOR 12 WEEKS. Treatment of HCV genotype 2 in treatment-experienced patients with or without cirrhosis · Sofosbuvir (400 mg/day) in combination with ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks or 16 weeks. · Sofosbuvir (400 mg/day) in combination with peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly plus ribavirin (1,000 mg/day if <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. Treatment of HCV genotype 3 in treatment-naïve and treatment-experienced patients without cirrhosis · Ledipasvir/sofosbuvir (90/400 mg/day) plus ribavirin (1,000mg/day if <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. · Sofosbuvir (400 mg/day) plus ribavirin (1,000 mg/day if <75 kg or 1,200 mg if ≥75 kg with food, in divided doses) for 24 weeks. Treatment of HCV genotype 3 in treatment-naïve patients with cirrhosis · Ledipasvir/sofosbuvir (90/400 mg/day) plus ribavirin (1,000mg/day if <75kg or

Clinical Guideline	Recommendation(s)
	1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. Treatment of HCV genotype 3 in treatment-experienced patients with cirrhosis · Sofosbuvir (400 mg/day) in combination with peginterferon alfa-2a 180 mcg subcutaneously weekly or alfa-2b 1.5 mcg/kg subcutaneously weekly plus ribavirin (1,000 mg/day if <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. Treatment of HCV genotype 4 in treatment-naïve and treatment-experienced patients with or without cirrhosis · Ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg): 2 tablets once daily in the morning with food + ribavirin (1,000 mg/day if <75kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks; dasabuvir not needed. NOT FDA APPROVED. Note: DO NOT USE if patient virologically failed DAA-based therapy. · Alternative regimen: Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily ± ribavirin for 12 weeks. NOT FDA APPROVED. · Alternative regimen: Sofosbuvir (400 mg/day): 1 tablet daily in combination with ribavirin (1,000 mg/day if <75 kg and 1,200 mg/day if ≥75 kg with food, in divided doses) and peginterferon for 12 weeks. Stopping rules based on lack of virologic response · Patients should have an HCV RNA level assessed at week 4 of treatment. · If the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered. · HCV RNA levels should be assessed at 12 weeks after completion of treatment to determine whether SVR was achieved. Use in HIV/HCV-coinfection · HIV/ HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients, provided the patient is receiving appropriate HIV care and drug-drug interactions are addressed appropriately. Treatment in pre-liver transplant · Genotype 1, including patients with CTP A, B, or C and suitable patients with HCC o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses including patients with CTP A; in CPT B and C patients, ribavirin 600 mg/day and increase by 200 mg/day every 2 weeks only as tolerated if hemoglobin remains above 10 g/dL) for 12 weeks. NOT FDA APPROVED. · Genotype 2, including patients including suitable patients with HCC o Sofosbuvir (400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg if ≥75 kg with food, in divided doses) for 24 to 48 weeks or until the time of transplantation, whichever occurs first. · Genotype 3 or 4 o Consult with a transplant center prior to starting treatment. In general, the preferred treatment is the same treatment as is recommended for treatment-naïve or treatment-experienced (as appropriate) patients. Treatment in post-liver transplant · Genotype 1

Clinical Guideline	Recommendation(s)
	o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. o If ribavirin intolerant: Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 24 weeks. NOT FDA APPROVED. · Genotype 2 o Sofosbuvir (400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 24 weeks. NOT FDA APPROVED. · Genotype 3 o The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or by specialists with extensive experience in the treatment of pre- or post-transplant patients. · Genotype 4 o Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily + ribavirin (1,000 mg/day if <75 kg or 1,200 mg/day if ≥75 kg with food, in divided doses) for 12 weeks. NOT FDA APPROVED. o If ribavirin intolerant: Ledipasvir/sofosbuvir (90/400 mg/day): 1 tablet daily for 24 weeks. NOT FDA APPROVED.
European Association for the Study of the Liver: **Treatment of Hepatitis (2015)**[35]	<u>Goals and endpoints of HCV therapy</u> · The goal of therapy is to cure HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extra-hepatic manifestations, and death. · The endpoint of therapy is SVR, defined by undetectable HCV RNA 12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients. · Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%. <u>Indications for treatment</u> · All treatment-naïve and –experienced patients with compensated or decompensated chronic liver disease due to HCV should be considered for therapy. · Treatment should be prioritized for patients with significant fibrosis or cirrhosis (F3 to F4). · Patients with decompensated cirrhosis (Child Pugh B or C) should be urgently treated with an interferon-free regimen. · Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, hemodialysis patients, and incarcerated individuals · Treatment is justified in patients with moderate fibrosis (F2). · In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized. · Treatment is not recommended in patients with limited life expectancy due to non-liver related comorbidities <u>Treatment considerations for HIV/HCV-coinfection</u> · Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection. · Interferon-free regimens are the best options when available in all HCV-monoinfected and in HIV-coinfected patients because of their virological efficacy, ease of use and tolerability. · The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine,

Clinical Guideline	Recommendation(s)
	nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir. · Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz. · No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs. · The fixed-dose combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/ cobicistat when possible, or used with caution with frequent renal monitoring. · The combination of ombitasvir/paritaprevir/ritonavir and dasabuvir should not be used with efavirenz, etravirine or nevirapine, and rilpivirine should be used cautiously with repeat electrocardiogram monitoring. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contraindicated with this combination. Elvitegravir/cobicistat should not be used with this regimen because of the additional boosting effect. <u>Treatment options for HCV genotype 1 infection</u> · Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. · Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). o Not recommended for HCV genotype 1a with Q80K polymorphism. o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week 4, 12 or 24. · Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (compensated cirrhosis) · Ledipasvir/sofosbuvir for eight weeks may be considered in treatment-naïve patients without cirrhosis and baseline HCV RNA <6 million. This should be done with caution especially in in patients with F3. · Ledipasvir/sofosbuvir and ribavirin for 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75,000/µL. · Ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks (HCV genotype 1b without cirrhosis) or with ribavirin for 12 weeks (HCV genotype 1b with cirrhosis or HCV genotype 1a without cirrhosis) · Ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 24 weeks (HCV genotype 1a with cirrhosis) · Sofosbuvir and simeprevir without ribavirin for 12 weeks (patients without cirrhosis) or with ribavirin for 12 weeks (cirrhotics) · Sofosbuvir and simeprevir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) · Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis) · Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) <u>Treatment options for HCV genotype 2 infection</u> · Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in cirrhotics, especially treatment-experienced). · Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients. · Daclatasvir and sofosbuvir for 12 weeks is an option for cirrhotic and/or

Clinical Guideline	Recommendation(s)
	treatment-experienced patients. Treatment options for HCV genotype 3 infection · Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (including patients who failed prior treatment with sofosbuvir and ribavirin) · Sofosbuvir plus ribavirin for 24 weeks o Suboptimal in treatment-experienced cirrhotics or those who failed prior treatment with sofosbuvir and ribavirin · Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin 24 weeks (cirrhosis, pending data with 12 weeks of therapy). Treatment options for HCV genotype 4 infection · Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. · Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics). o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week 4, 12 or 24. · Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis) · Ledipasvir/sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) · Ledipasvir/sofosbuvir with ribavirin for 24 weeks is an option in treatment-experienced cirrhotics and negative predictors of response, such as a platelet count <75,000/µL. · Ombitasvir/paritaprevir/ritonavir and ribavirin for 12 weeks (no cirrhosis) or for 24 weeks (cirrhosis) · Sofosbuvir and simeprevir without ribavirin for 12 weeks (patients without cirrhosis) or with ribavirin for 12 weeks (cirrhotics) · Sofosbuvir and simeprevir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) · Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis). · Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) Treatment options for HCV genotype 5 or 6 infection · Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. · Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (compensated cirrhosis) · Ledipasvir/sofosbuvir for 24 weeks (cirrhotic patients with contraindication or intolerance to ribavirin) · Ledipasvir/sofosbuvir and ribavirin for 24 weeks (treatment-experienced cirrhotics with negative predictors of response, such as a platelet count <75,000/µL). · Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis). · Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) Treatment monitoring · A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor HCV RNA levels during and after therapy.

Clinical Guideline	Recommendation(s)
	· In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy. · In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week 4, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy. · In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment in patients treated 12 or 24 weeks, respectively), and 12 or 24 weeks after the end of therapy. <u>Stopping (futility) rules</u> · Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥25 IU/mL at treatment week 4, 12 or 24; an immediate switch to another interferon-containing direct-acting antiviral-containing or an interferon-free regimen without a protease inhibitor should be considered · No futility rules have been defined for other treatment regimens. <u>Virological response-guided triple therapy</u> · With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks. · Patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24. · No response-guided therapy is used in other treatment regimens. <u>Measures to improve treatment adherence</u> · HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy. · Counseling on the importance of adherence is recommended. · In persons who actively inject drugs, access to harm reduction programs is mandatory. · Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. · HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. <u>Retreatment of non-sustained virological responders</u> · HCV genotype 1 patients who failed telaprevir or boceprevir plus peginterferon alfa and ribavirin should be retreated with ledipasvir/sofosbuvir, or daclatasvir and sofosbuvir, with ribavirin for 12 weeks. · Recommendations for retreatment after failure of second-wave direct-acting antiviral-based anti-HCV regimens are based on indirect evidence and subject to change when more data become available. · Patients who failed on a second-wave direct-acting-antiviral-containing regimen, with or without peginterferon alfa or ribavirin, should be retreated with an interferon-free regimen for 12 weeks with weight-based ribavirin; extending therapy to 24 weeks with ribavirin may be considered, especially in patients with

Clinical Guideline	Recommendation(s)
	liver fibrosis stage F3 or F4. · Patients who failed on sofosbuvir alone or sofosbuvir plus ribavirin or sofosbuvir plus peginterferon alfa and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir (genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6), or with ombitasvir/paritaprevir/ritonavir and dasabuvir (genotype 1), or with ombitasvir/paritaprevir/ritonavir (genotype 4). · Patients infected with genotype 1 or 4 who failed on a regimen combining peginterferon alfa, ribavirin and simeprevir should be retreated with daclatasvir plus sofosbuvir or ledipasvir/sofosbuvir. · Patients who failed on a regimen combining peginterferon alfa, ribavirin and daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 or 4). Patients infected with other genotypes should be retreated with daclatasvir plus sofosbuvir (genotypes 2, 3, 5 and 6) or ledipasvir/sofosbuvir (genotypes 5 and 6). · Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated with daclatasvir plus sofosbuvir of ledipasvir/sofosbuvir. · Patients who failed on a regimen containing daclatasvir and sofosbuvir or ledipasvir/sofosbuvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4); patients infected with other genotypes should be retreated with the combination of daclatasvir and sofosbuvir (genotypes 2, 3, 5 and 6) or with the combination of ledipasvir/sofosbuvir (genotypes 5 and 6) for 24 weeks. · Patients infected with genotype 1 who failed ombitasvir/paritaprevir/ritonavir and dasabuvir should be retreated with a sofosbuvir-based regimen (e.g., sofosbuvir and simeprevir, daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir. · Patients infected with genotype 4 who failed ombitasvir/paritaprevir/ritonavir should be retreated with a sofosbuvir-based regimen (e.g., sofosbuvir and simeprevir, daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir). · Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available. · The efficacy and safety of a triple combination regimen including sofosbuvir, an NS3 protease inhibitor and an NS5A protease inhibitor in patients who failed on a direct-acting antiviral-containing regimen is unknown. · The utility of HCV resistance testing prior to retreatment in patients who failed on any of the direct-acting antiviral-containing treatment regimens is unknown. <u>Treatment of patients with severe liver disease</u> · Patients with decompensated cirrhosis (Child-Pugh B and Child-Pugh C) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), ledipasvir/sofosbuvir (genotypes 1, 4, 5 and 6), or daclatasvir plus sofosbuvir (all genotypes), with weight-based ribavirin, for 12 weeks. · Patients with decompensated cirrhosis with contraindication or intolerance to ribavirin should receive ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6), or daclatasvir plus sofosbuvir (all genotypes) for 24 weeks. <u>Patients with an indication for liver transplantation</u> · In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection. · Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation.

Clinical Guideline	Recommendation(s)
	· Patients awaiting liver transplantation should be treated with an interferon-free regimen, in principle for 12 or 24 weeks, practically up to transplantation, with ribavirin. · Patients with conserved liver function (Child-Pugh A) in whom the indication for transplantation is hepatocellular carcinoma can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), with ledipasvir/sofosbuvir and ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a), with ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks (genotype 4), with sofosbuvir plus simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes). · Treatment with sofosbuvir plus interferon alfa and ribavirin for 12 weeks is acceptable in patients with compensated (Child-Pugh A) cirrhosis awaiting liver transplantation if interferon-free options are not available. · Patients with decompensated cirrhosis (Child-Pugh B or C) awaiting liver transplantation can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes); however, data are limited in patients with Child-Pugh C cirrhosis >12 points or with a MELD score >20. · The optimal timing of treatment (before transplantation or post-transplantation) to maximize survival is still debatable and requires individual assessment. <u>Post-liver transplantation recurrence</u> · Patients with post-transplant recurrence of HCV infection should be considered for therapy. · Patients with post-transplant recurrence of HCV should be treated with an interferon-free regimen, for 12 or 24 weeks with ribavirin. · Patients without cirrhosis or with compensated (ChildPugh A) cirrhosis post-transplant can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir/sofosbuvir with ribavirin for 12 weeks (all genotypes), without the need for immunosuppressant drug dose adjustments. · Patients without cirrhosis or with compensated (ChildPugh A) cirrhosis post-transplant can be treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a with cirrhosis), with ombitasvir/paritaprevir/ritonavir for 12 or 24 weeks with ribavirin (genotype 4 without or with cirrhosis, respectively), or with sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), with the need for immunosuppressant drug dose adjustments or, in the case of the sofosbuvir and simeprevir combination, the need to avoid cyclosporine A. · Patients with decompensated (Child-Pugh B or C) cirrhosis can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance. · No dose adjustment is required for tacrolimus or cyclosporine with sofosbuvir and ribavirin, ledipasvir/sofosbuvir or daclatasvir plus sofosbuvir. · Because of significantly increased plasma concentrations of simeprevir, the concomitant use of simeprevir and cyclosporine A is not recommended in liver transplant recipients; no simeprevir dose changes are required with tacrolimus

Clinical Guideline	Recommendation(s)
	and sirolimus, but regular monitoring of their blood concentrations should be performed. · When using the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir, the tacrolimus and cyclosporine A doses must be adjusted; prednisone use at doses ≤5 mg/ day is permitted, but the use of mTOR inhibitors is not recommended. Hepatitis B virus (HBV) co-infection · Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. · If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. Immune complex-mediated manifestations of chronic hepatitis C · Treatment of HCV-associated lymphoma should utilize new interferon-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known. The effect of new antiviral therapies together with B cell depletion requires further study. An interdisciplinary approach with close monitoring of liver function is required. · Appropriate antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection. The role of rituximab in HCV-related renal disease requires evaluation. The more rapid inhibition of HCV replication and high SVR rates will need correlation with the response of the renal injury and the cryoglublinemia. Careful monitoring for adverse events is mandatory. Hemodialysis patients · Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. · Hemodialysis patients should receive an interferon alfa-free, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis · Simeprevir, daclatasvir, and ombitasvir/paritaprevir/ritonavir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease · Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available · The need for dose adjustments for the approved HCV direct-acting antivirals in patients on dialysis is unknown. No safety dosing and efficacy data is available in this population. These drugs should thus be used with extreme caution in patients with severe renal disease, and only in extreme life-threatening situations for patients on dialysis. Non-hepatic solid organ transplant recipients · HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. · Where possible, interferon-free and ribavirin-free antiviral regimen for 12 weeks in patients without cirrhosis, for 24 weeks in patients with compensated (Child-Pugh A) cirrhosis, following the above recommendations, should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population, and the need for dose adjustments for the new direct-acting antivirals is unknown. · These drugs should thus be used with extreme caution and sofosbuvir should

Clinical Guideline	Recommendation(s)
	not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available. · In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen, following the above recommendations on treatment regimen and management of drug-drug interactions with cyclosporine and tacrolimus when appropriate. Active drug addicts and patients on stable maintenance substitution · HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. · Evaluation of safety and efficacy of new interferon-containing and interferon-free regimens in PWIDs is needed. · The anti-HCV regimens that can be used in PWIDs are the same as in non-PWIDs. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. · PWIDs on opioid substitution therapy should receive an interferon-free regimen Treatment of acute hepatitis C · Peginterferon alfa monotherapy for 12 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. · Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection. · Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates.

Conclusions

The direct acting hepatitis C antiviral and combination products are all Food and Drug Administration (FDA)-approved for the treatment of chronic hepatitis C virus (HCV) infection; although, differences in indications exist relating to use in specific genotypes, with certain combination therapies and other patient factors.[1-6] Efficacy of these agents have been established in multiple clinical trials with numerous clinical trials still underway.[11-33] Newly published guidelines developed by the American Association for the Study of Liver Diseases, Infectious Diseases Society of America and International Antiviral Society-USA have included all current treatments in their recommendations.[33] Generally speaking, combination regimens that include newer direct hepatis C antivirals are preferred over older pegylated interferon-based regimens (including those containing older protease inhibitors) due to a higher sustained virologic response (SVR) rate, improved side effects profile, and reduced pill burden. However, many different regimens with direct-acting agents or combinations, which may or may not also include ribavirin or pegylated interferon, are recommended based on HCV genotype, previous treatment experience and certain special populations. These regimens along with other clinical guidelines are summarized in Table 12.[33-35] Currently, there are no generic direct-acting antivirals available.

References

1. Daklinza® [package insert]. Princeton (NJ): Bristol-Myers Squibb Company; 2015 July [cited 2015 July 30]. Available from: http://packageinserts.bms.com/pi/pi_daklinza.pdf.
2. Olysio® [package insert]. Titusville (NJ): Janssen Therapeutics; 2014 Nov.
3. Sovaldi® [package insert]. Foster City (CA): Gilead Sciences, Inc.; 2014 Nov.
4. Harvoni® [package insert]. Foster City (CA): Gilead Sciences, Inc.; 2014 Oct.
5. Viekira Pak® [package insert]. North Chicago (IL): AbbVie; 2014 Dec.
6. Technivie® [package insert on the internet]. North Chicago (IL): AbbVie; 2015 July [cited 2015 Aug 4]. Available from: https://www.technivie.com/.
7. Micromedex® 2.0 [database on the Internet]. Greenwood Village (CO): Truven Health Analytics; Updated periodically [cited 2015 Jan 21]. Available from http://www.micromedexsolutions.com/.
8. Workowski KA, Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. MMWR Recomm Rep. 2010 Dec 17;59(RR-12):1-110.
9. Ghany MG, Strader DB, Thomas DL, Seeff LB; American Association for the Study of Liver Diseases. Diagnosis, Management and treatment of hepatitis C; An Update. 2009. Hepatology 2009; 49(4):1-40.
10. Ng J, Wu J. Hepatitis B- and hepatitis C-related hepatocellular carcinomas in the United States: similarities and differences. Hepat Mon. 2012 Oct;12(10 HCC):e7635.
11. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med. 2013 May 16;368(20):1878-87.
12. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014 May 15;370(20):1889-98.
13. Kowdley KV, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med. 2014 May 15;370(20):1879-88.
14. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1594-603.
15. Ferenci P, Bernstein D, Lalezari J, Cohen D, Luo Y, Cooper C, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014 May 22;370(21):1983-92.
16. Poordad F, Hezode C, Trinh R, Kowdley KV, Zeuzem S, Agarwal K, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014 May 22;370(21):1973-82.
17. Afdhal N, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med. 2014 Apr 17;370(16):1483-93.
18. Lawitz E, Sulkowski MS, Ghalib R, Rodriguez-Torres M, Younossi ZM, Corregidor A, et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet. 2014 Jul 26. pii: S0140-6736(14)61036-9.
19. Zeuzem S, Jacobson IM, Baykal T, Marinho RT, Poordad F, Bourlière M, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014 Apr 24;370(17):1604-14.
20. Andreone P, Colombo MG, Enejosa JV, Koksal I, Ferenci P, Maieron A, et al. ABT-450, Ritonavir, Ombitasvir, and Dasabuvir Achieves 97% and 100% Sustained Virologic Response With or Without Ribavirin in Treatment-Experienced Patients With HCV Genotype 1b Infection. Gastroenterology. 2014 May 9.
21. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014 Dec 18;371(25):2375-82.
22. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013 May 16;368(20):1867-77.
23. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes
24. Nelson DR, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. Hepatology. 2015 Apr;61(4):1127-35.
25. Bristol-Myers Squibb. Safety and Efficacy Study of Daclatasvir 60mg, Sofosbuvir 400mg, and Ribavirin (Dosed Based Upon Weight) in Subjects With Chronic Genotype 3 Hepatitis C Infection With or Without Prior Treatment Experience and Compensated Advanced Cirrhosis for 12 or 16 Weeks. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02319031 NLM Identifier: NCT02319031.

26. Hézode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, et al. Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial. Lancet. 2015 Jun 20;385(9986):2502-9.
27. AbbVie. A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir Co-administered With Ribavirin (RBV) in Adults With Genotype 4 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis (AGATE-1). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02265237 NLM Identifier: NCT02265237.
28. AbbVie. A Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir with Ribavirin in Adults with Genotype 1 and Ombitasvir/Paritaprevir/Ritonavir with Ribavirin in Adults with Genotype 4 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis (TURQUOISE-CPB). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02219477 NLM Identifier: NCT02219477.
29. AbbVie. Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir in Adults with Genotype 1a or Genotype 4 Chronic Hepatitis C Virus (HCV) Infection, with Severe Kidney Impairment or End Stage Kidney Disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02487199 NLM Identifier: NCT02487199.
30. AbbVie. Ombitasvir/Paritaprevir/Ritonavir with or without Dasabuvir in Adults with Genotype 1a or Genotype 4 Chronic Hepatitis C Virus (HCV) Infection, With Severe Kidney Impairment or End Stage Kidney Disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02487199 NLM Identifier: NCT02487199.
31. AbbVie. A Study to Evaluate Treatment of Hepatitis C Virus Infection in Pediatric Subjects (Zircon). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02486406 NLM Identifier: NCT02486406.
32. AbbVie. A Study to Evaluate the Safety and Efficacy of Ombitasvir/Paritaprevir/r with or without Dasabuvir and with Ribavirin in Chronic Hepatitis C Virus Genotype 1 or 4 Infected Adults with Successfully Treated Early Stage Hepatocellular Carcinoma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2015 Aug 5]. Available https://clinicaltrials.gov/ct2/show/NCT02504099 NLM Identifier: NCT02504099.
33. American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), International Antiviral Society-USA (IAS-USA). Recommendations for testing, managing, and treating hepatitis C [guideline on the Internet]. Alexandria (VA): AASLD/IDSA/IAS-USA 2015 Aug [cited 2015 Aug 10]. Available at: http://www.hcvguidelines.org.
34. Department of Veteran Affairs National Hepatitis C Resource Center Program and the Office of Public Health. Chronic hepatitis C Virus (HCV) infection: Treatment considerations [guideline on the Internet]. Washington (DC): VA 2015 July [cited 2015 July 31]. Available at: http://www.hepatitis.va.gov/pdf/treatment-considerations-2015-07.pdf.
35. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015 Jul;63(1):199-236.
36. Pegasys® [package insert]. South San Francisco (CA): Genentch USA, Inc.; 2013 Jul.
37. PegIntron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2015 Jan.
38. Sylatron® [package insert]. Whitehouse Station (NJ): Merck & Co., Inc.; 2014 Nov.
39. Copegus® [package insert]. South San Francisco (CA): Genentech, Inc.; 2013 Feb.
40. Moderiba® [package insert]. North Chicago (IL): AbbVie Inc.; 2014 Nov.
41. Moderiba Pak® [package insert]. North Chicago (IL): AbbVie Inc.; 2014 Nov.
42. Rebetol® [package insert]. Whitehouse Station (NJ): Schering-Plough Corporation; 2014 Jun.
43. Ribasphere® [package insert]. Warrendale (PA): Kadmon Pharmaceuticals, LLC; 2014 Dec.
44. Ribasphere RibaPak® [package insert]. Warrendale (PA): Kadmon Pharmaceuticals, LLC; 2014 Dec.

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Daklinza (daclatasvir) is subject to prior authorization.

1. Coverage and limitations:

   Authorization will be given if the following criteria are met and documented:
   a. The recipient has a diagnosis of hepatitis C genotype 3
      AND
   b. Recipient is ≥ 18 years of age
      AND
   c. The recipient has not had a liver transplant
      AND
   d. The requested agent will be used in combination with Sovaldi
      AND
   e. The recipient is not on a strongCYP3A inducer
      AND
   f. The recipient does not have cirrhosis (Metavir score F4).
      AND
   g. One of the following:
      i. The requested dose of Daklinza is 60 mg (one tablet) daily
         OR
      ii. The requested dose of Daklinza is 30 mg (one tablet) daily and the recipient is receiving a concomitant strong CYP3A inhibitor
         OR
      iii. The requested dose of Daklinza is 90 mg (one 30 mg tablet and one 60 mg tablet) daily and the recipient is receiving a concomitant moderate CYP3A inducer. Medical necessity of continued use of the moderate CYP3A inducer during Daklinza therapy must be provided.

      AND
   h. The requested length of therapy is 12 weeks

2. Prior Authorization Guidelines:
   a. Prior Authorization approval length will be for 12 weeks

3. Quantity Limitations:
   a. 28 tablets/28 days

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Technivie (ombitasvir/paritaprevir/ritonavir) is subject to prior authorization.

1. Coverage and limitations:

   Authorization will be given if the following criteria are met and documented:
   a. Diagnosis of chronic hepatitis C genotype 4
      AND
   b. Member is ≥ 18 years of age
      AND
   c. The recipient does not have cirrhosis (Metavir score F4)
      AND
   d. The recipient does not have moderate or severe hepatic impairment (Child-Pugh grade B or C)
      AND
   e. For treatment-naïve recipients:
      i. Technivie will be used in combination with ribavirin
         OR
      ii. Technivie will be used without ribavirin and there is documentation that the recipient cannot take or cannot tolerate ribavirin
      AND
   f. For treatment-experienced recipients, Technivie will be used in combination with ribavirin
      AND
   g. The requested dose is two Technivie tablets daily
      AND
   h. Total duration of therapy does not exceed 12 weeks

2. Prior Authorization Guidelines:
   a. Prior Authorization approval length will be for 12 weeks

3. Quantity Limitations:
   a. 2 boxes (56 tablets)/28 days

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Olysio® (simeprevir) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
   Approval for Olysio® (simeprevir) will be given if the following criteria are met and documented:

   a. The recipient has a diagnosis of chronic hepatitis C genotype 1 infection;

      AND

   b. The recipient has not received a previous course of therapy with Incivek® (telaprevir), Olysio® (simeprevir), or Victrelis® (boceprevir) unless the drug is being switched due to an adverse event with the alternative drug;

      AND

   c. One of the following:
      1. The recipient will be treated concomitantly with peginterferon alfa plus ribavirin and meets **one** of the following:

         a. For treatment initiation (treatment weeks one through eight), the recipient has been pre-screened and does not test positive for the 1A NS3 Q80K polymorphism.

         b. For treatment continuation (treatment weeks nine through 12), the recipient must have **one** of the following:

            i. The recipient is treatment-naïve, and their HCV-RNA level was <25 IU/mL at treatment week four; **or**

            ii. The recipient is a previous prior relapser and their HCV-RNA level was <25 IU/mL at treatment week four; **or**

            iii. The recipient is a partial or a null-responder to previous therapy of interferon and ribavirin alone (no other HCV protease inhibitors) and their HCV-RNA was <25 IU/mL at treatment week four.

      OR

      2. The recipient will be treated concomitantly with sofosbuvir

2. PA Guidelines:

a. Prior Authorization approval will be for 12 weeks for recipients who will be treated concomitantly with sofosbuvir and who do not have cirrhosis.

b. Prior Authorization approval will be for a total of 24 weeks for recipients who will be treated concomitantly with sofosbuvir and have cirrhosis.

c. For recipient will be treated concomitantly with peginterferon alfa plus ribavirin:

    1. Initial authorization approval will be for eight weeks.

    2. For recipients meeting criteria for continuation treatment for treatment weeks nine through 12, a prior authorization approval may be renewed once for an additional four weeks.

d. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

3. Quantity Limitations:
1 tablet/day

DIVISION OF HEALTH CARE FINANCING AND POLICY
NEVADA MEDICAID
DRUG USE REVIEW (DUR) BOARD
PROPOSED PRIOR AUTHORIZATION CRITERIA

Sovaldi® (sofosbuvir) is a covered benefit of Nevada Medicaid for recipients who meet the criteria for coverage.

1. Coverage and Limitations:
   Approval for Sovaldi® (sofosbuvir) for mono-infected or HCV/HIV-1 co-infected recipients will be given if **one** the following criteria are met and documented:

   a. The recipient has a diagnosis of hepatitis C genotype 1 and will be treated with peginterferon alfa and ribavirin and ribavirin or, if the recipient is ineligible to receive peginterferon alfa, in combination with ribavirin;

      OR

   b. The recipient has a diagnosis of Chronic Hepatitis C Genotype 2 or 3 Infection; and the recipient will be treated in combination with ribavirin;

      OR

   c. The recipient has a diagnosis of Chronic Hepatitis C Genotype 4 Infection; and the recipient will be treated in combination with peginterferon alfa and ribavirin;

      OR

   d. The recipient has a diagnosis of Chronic Hepatitis C Genotype 1, 2, 3, or 4 infection; and the recipient has a diagnosis of hepatocellular carcinoma and is awaiting a liver transplant; and the recipient will be treated in combination with ribavirin;

      OR

   e. The recipient has a diagnosis of chronic hepatitis C Genotype 1 infection and will be treated in combination with simeprevir.

      OR

   f. The recipient has a diagnosis of chronic hepatitis C Genotype 3 infection and will be treated in combination with daclatasvir.

2. PA Guidelines:

   a. Prior Authorization approval will be for 12 weeks for ALL of the following:

      1. Recipients with a diagnosis of Chronic Hepatitis C Genotype 1 infection and combination therapy with peginterferon alfa and ribavirin.

2. Recipients with a diagnosis of Chronic Hepatitis C Genotype 2 infection and combination therapy with ribavirin.

3. Recipients with a diagnosis of Chronic Hepatitis C Genotype 4 infection and combination therapy with peginterferon and ribavirin.

4. Recipients with a diagnosis of Chronic Hepatitis C Genotype 1 infection who do not have cirrhosis and combination therapy with simeprevir.

5. Recipients with a diagnosis of Chronic Hepatitis C Genotype 3 infection who do not have cirrhosis.

b. Prior Authorization approval will be for 24 weeks for all of the following:

1. Recipients with a diagnosis of Chronic Hepatitis C Genotype 1 infection and combination therapy with ribavirin.

2. Recipient with a diagnosis of Chronic Hepatitis C Genotype 3 infection and combination therapy with ribavirin.

3. Recipients with a diagnosis of Chronic Hepatitis C Genotype 1 infection who have cirrhosis and combination therapy with simeprevir.

c. Prior Authorization approval will be for up to 48 weeks or until liver transplantation for recipients with a diagnosis of hepatocellular carcinoma and is awaiting a liver transplant combination therapy with ribavirin. Requests will be approved in 24 week intervals

d. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

3. Quantity Limitations:
1 tablet/day